XX Riunione Nazionale del Gruppo I.T.M.O.

Gastrointestinal Oncology
Targets and Drugs

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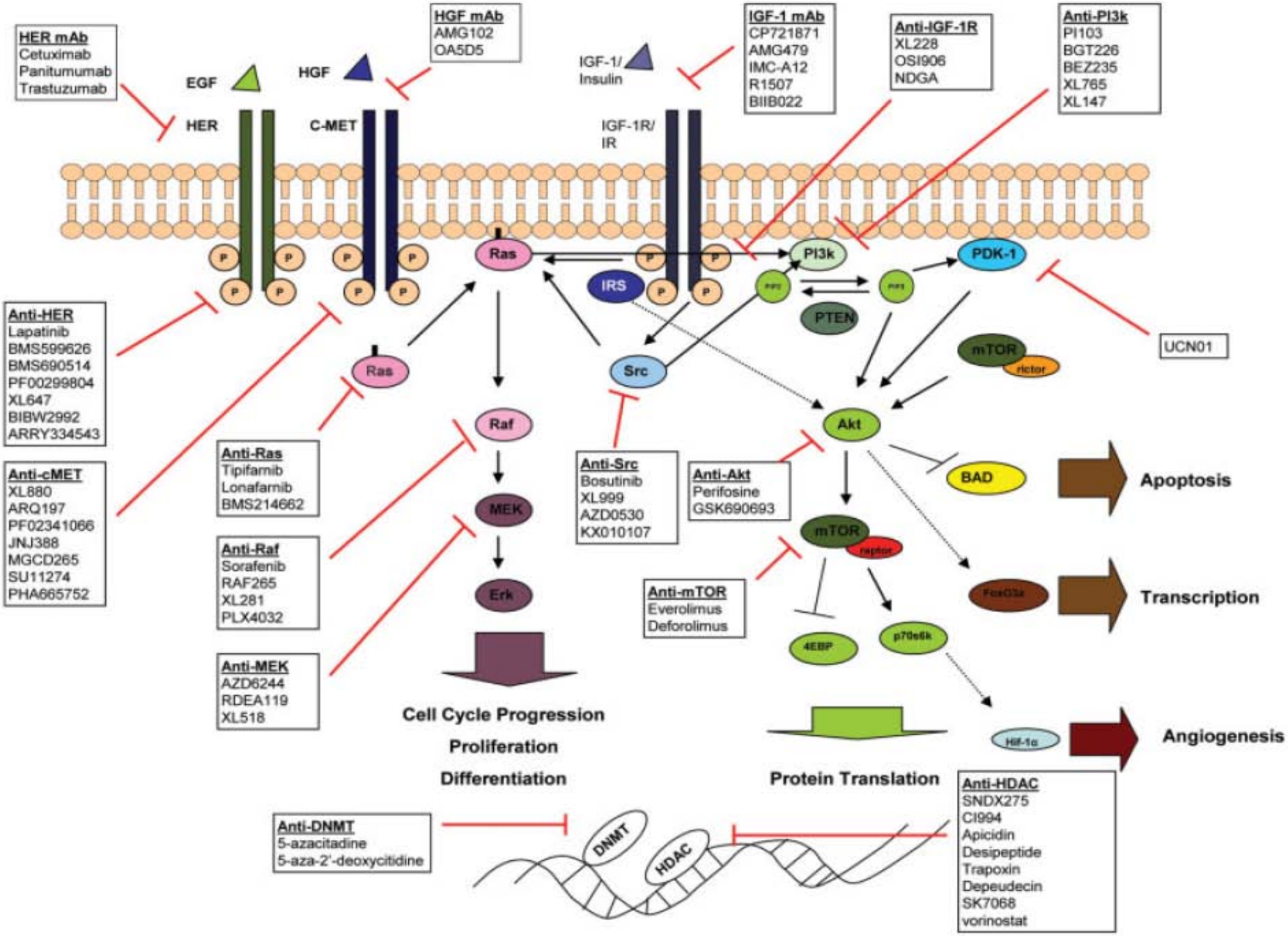
HER mAb
Cetuximab
Panitumumab
Trastuzumab
HGF mAb
AMG102
OA5D5
IGF-1 mAb
CP721871
AMG479
IMC-A12
R1507
BIIB022
Anti-IGF-1R
XL228
OSI906
NDGA
Anti-PI3k
PI103
BGT226
BEZ235
XL765
XL147
EGF
HGF
IGF-1/
Insulin
HER
C-MET
IGF-1R/
IR
Ras
PI3k
PDK-1
IRS
PIP2
PIP3
PTEN
mTOR
rictor
Src
Akt
UCN01
Anti-HER
Lapatinib
BMS599626
BMS690514
PF00299804
XL647
BIBW2992
ARRY334543
Ras
Raf
Anti-Ras
Tipifarnib
Lonafarnib
BMS214662
Anti-Src
Bosutinib
XL999
AZD0530
KX010107
Anti-Akt
Perifosine
GSK690693
BAD
Apoptosis
Anti-cMET
XL880
ARQ197
PF02341066
JNJ388
MGCD265
SU11274
PHA665752
MEK
Anti-Raf
Sorafenib
RAF265
XL281
PLX4032
mTOR
raptor
Anti-mTOR
Everolimus
Deforolimus
FoxO3a
Transcription
Erk
4EBP
p70s6k
Anti-MEK
AZD6244
RDEA119
XL518
Cell Cycle Progression
Proliferation
Differentiation
Protein Translation
Hif-1α
Angiogenesis
Anti-DNMT
5-azacitadine
5-aza-2'-deoxycitidine
DNMT
HDAC
Anti-HDAC
SNDX275
CI994
Apicidin
Desipeptide
Trapoxin
Depeudecin
SK7068
vorinostat

What can the molecular pathologist offer for optimal decision making?

S. D. Richman[1], G. G. A. Hutchins[1], M. T. Seymour & P. Quirke*

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Annals of Oncology 21 (Supplement 7): vii123–vii129, 2010
doi:10.1093/annonc/mdq379

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Table 1. Colorectal cancer sub-groups defined by molecular and morphological features

Feature	Group 1	Group 2	Group 3	Group 4	Group 5
MSI	High	Stable/low	Stable/low	Stable	High
Methylation	+++	+++	++	+/–	+/–
Ploidy	Dip > An	Dip > An	An > Dip	An > Dip	Dip > An
APC	+/–	+/–	+	+++	++
KRAS	–	+	+++	++	++
BRAF	+++	++	–	–	–
TP53	–	+	++	+++	+
Location	Right > left	Right > left	Left > right	Left > right	Right > left
Gender	F > M	F > M	M > F	M > F	M > F
Precursor	SP	SP	SP/AD	AD	AD
Serration	+++	+++	+	+/–	+/–
Mucinous	+++	+++	+	+	++
Necrosis	+	+	?	+++	+
Poor diff	+++	+++	+	+	++
Circumscribed	+++	+	?	++	++
Budding	+/–	+	?	+++	+
Lymphocytes	+++	+	?	+	+++

Marker	Drug	Malignancy	Clinical Implication	Comment	Genotypic Variation
DPYD (dihydropyrimidine dehydrogenase)	5-Fluorouracil	Colorectal, stomach, pancreatic cancer, head and neck, cervix, and breast	DPD deficiency is associated with higher risk of toxicity. IVS14+1G>A is the most important mutation causing severe toxicity or death.	Low sensitivity and specificity in predicting chemosensitivity. Phenotyping may be better.	Many different polymorphisms: IVS14 + 1G>A, DPYD *2A is a SNP that results in the skipping of exon 14 with resulting deficiency. It Is always associated with high toxicity.
TYMS (Thymidylate synthase)	5-Fluorouracil, capecitabine and Antimetabolites (TYMS TSER) pemetrexed	Colorectal, stomach, pancreatic cancer, NSCLC	High TYMS expressers may show poor response and less toxicity than low TYMS expressers, high TS expression is associated with a poor response to pemetrexed in NSCLC	Evaluation of TS expression status and TYMS haplotype would be more helpful. Clinical validation in additional prospective studies is needed before using TYMS genotype for clinical decision-making	3 main polymorphisms: 1. 6 bp deletion or insertion in the 3'-UTR (TYMS 1494); 2. 28 bp tandem repeat in the 5'-UTR enhancer region (TSER) (2R or 3R, TSER *2 or TSER *3) (TYMS-ER); 3. G>C single-nucleotide substitution within the second repeat of 3R (3RG or 3RC).
UGT1A1 (UDP glucoronyltransferase)	Irinotecan (Camptosar)	colorectal cancer	Decreased UGT1A1 activity may increase the risk of toxicity	Genotyping is useful for dosage regimens> 250mg/m2. Functional significance of variant alleles other than *28 remains unclear. Given the cumulative clinical evidence, the FDA revised the safety labelling for irinotecan in 2005, reccomending that treatment be altered for individuals who are homozygous for the UGT1A1 *28 allele.	The most well-studied variants: 1. UGT1A1 *28 (a 7-TA repeat sequence in the promoter region) 2. UGT1A1 *6 (226G>A, rs4148323)
GSTP1 (glutathione S-transferase P1)	5-Fluorouracil- and Oxaliplatin-based chemotherapy	Colorectal, stomach cancer and breast (?)	Patients with the Ile105Val variant allele may be less capable of detoxifying oxaliplatin (enhance drug elimination). But biochemical studies are needed to prove it. The GSTP1 105Val/105Val genotype is associated with higher response rate to oxalipaltin-based chemotherapy	Clinical validation in additional studies is needed	Polymorphism: A/G SNP, located in the substrate-binding domain resulting in aa substitution of Ile105Val, diminishes GSTP1 enzymtic activity
MLH1/MSH2 (Mismatch repair proteins)	5-Fluorouracil- and oxaliplatin-based chemotherapy	Colorectal cancer (sporadic)	IHC analysis of MLH1 and MSH2 expression is prognostic but not predictive for adjuvant 5-FU-based chemotherapy. MSI-H may be correlated with a poorer response to 5-FU/oxaliplatin	Additional prospective studies are needed	MSI-H analysis (high level microsatellite instability): 1. IHC analysis 2. PCR analysis MLH1: -93>A
ERCC, XRCC, and XPD	Oxaliplatin, Cisplatin and platinum-based chemotherapy	Colorectal, stomach cancer, breast, NSCLC	Polymorphisms in three major nucleotide excision repair genes my affect the function of this pathway.	Although extensively studied, the data have not led to any definitive conclusions.	XRCC1 1. Arg399Gln ERCC1: 1. C118T; C8092A (lower rate of translation) ERCC2: 1. K751Q

Implementing prognostic and predictive biomarkers in CRC clinical trials

Sandra Van Schaeybroeck, Wendy L. Allen, Richard C. Turkington and Patrick G. Johnston

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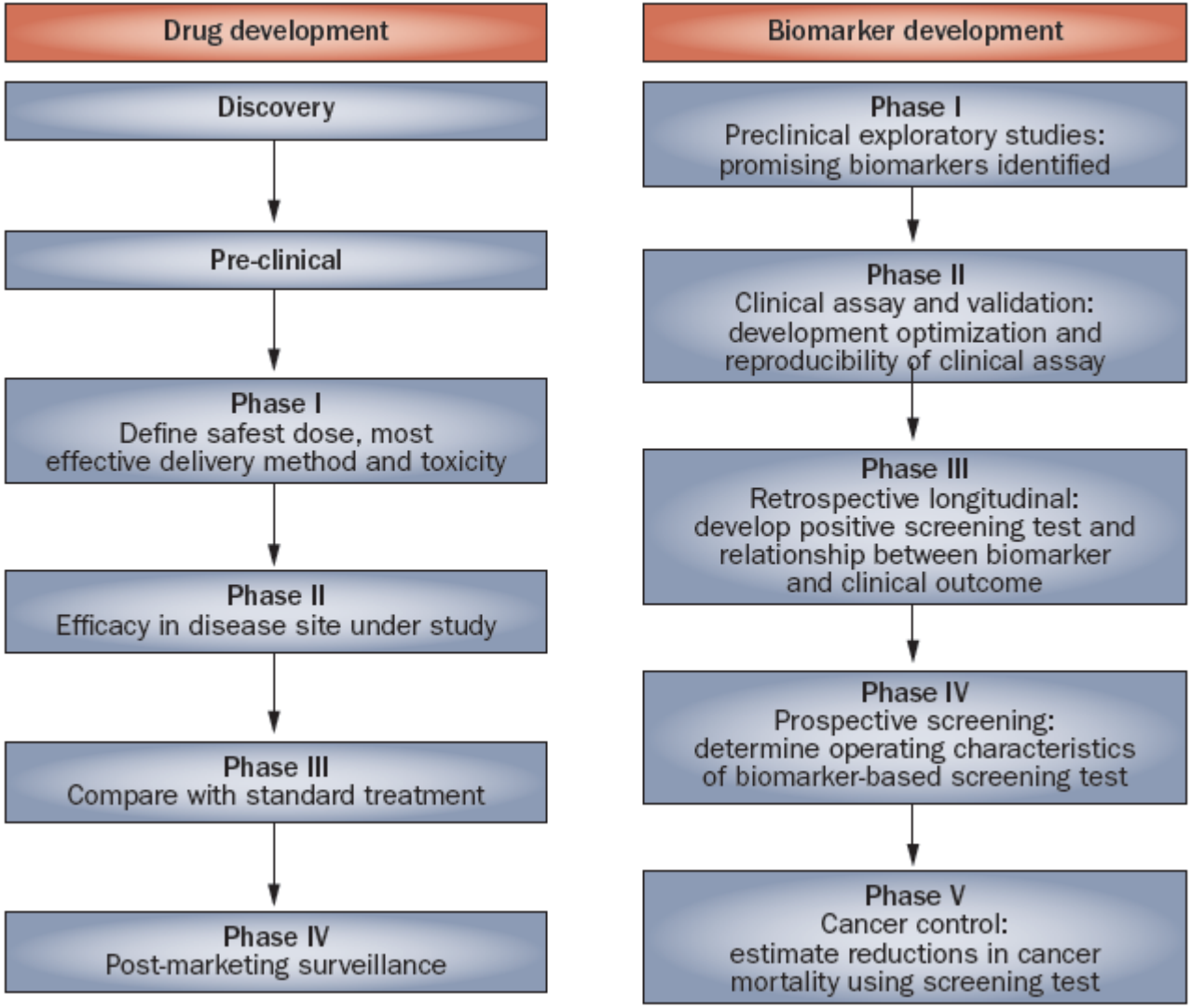
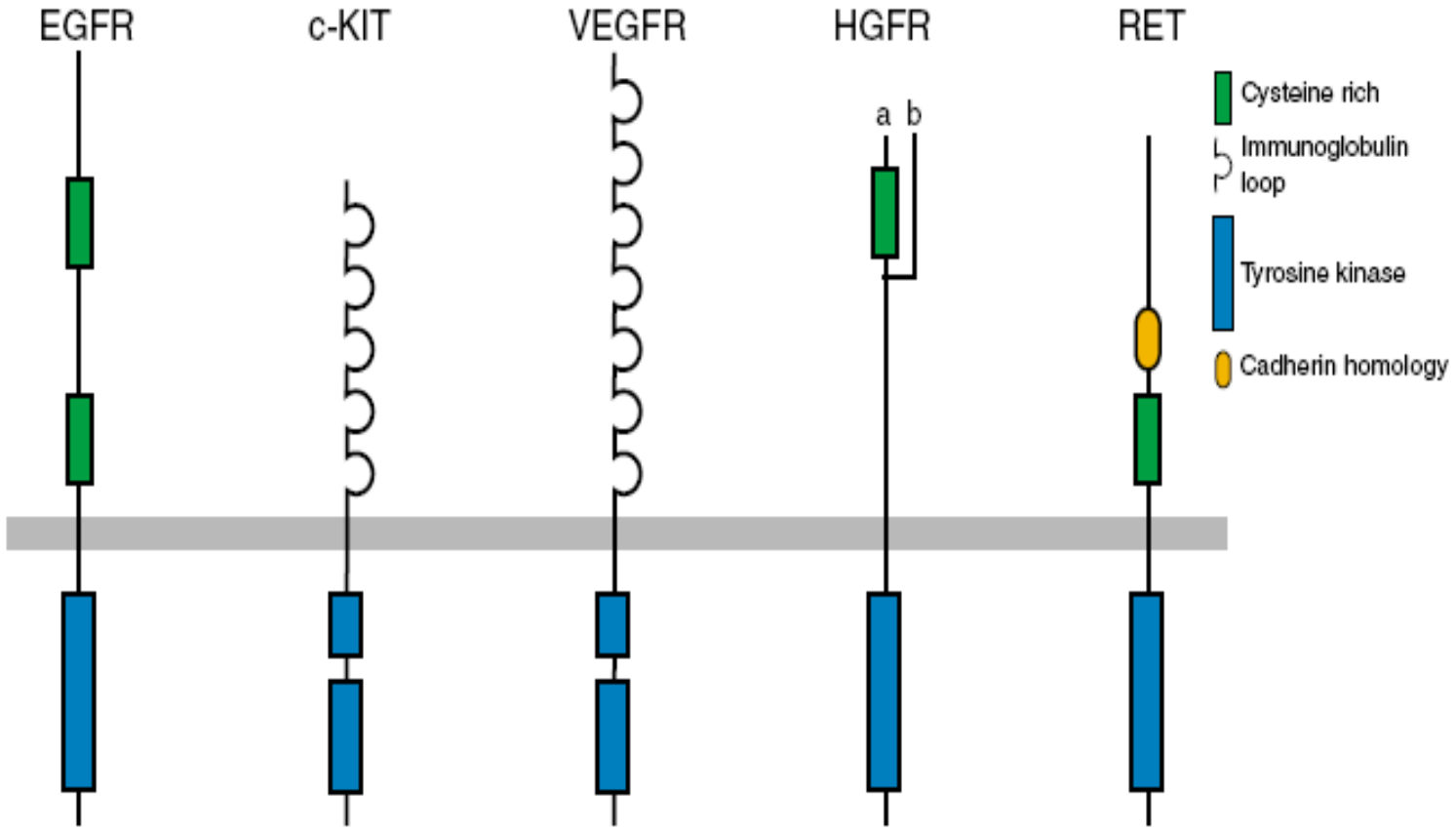
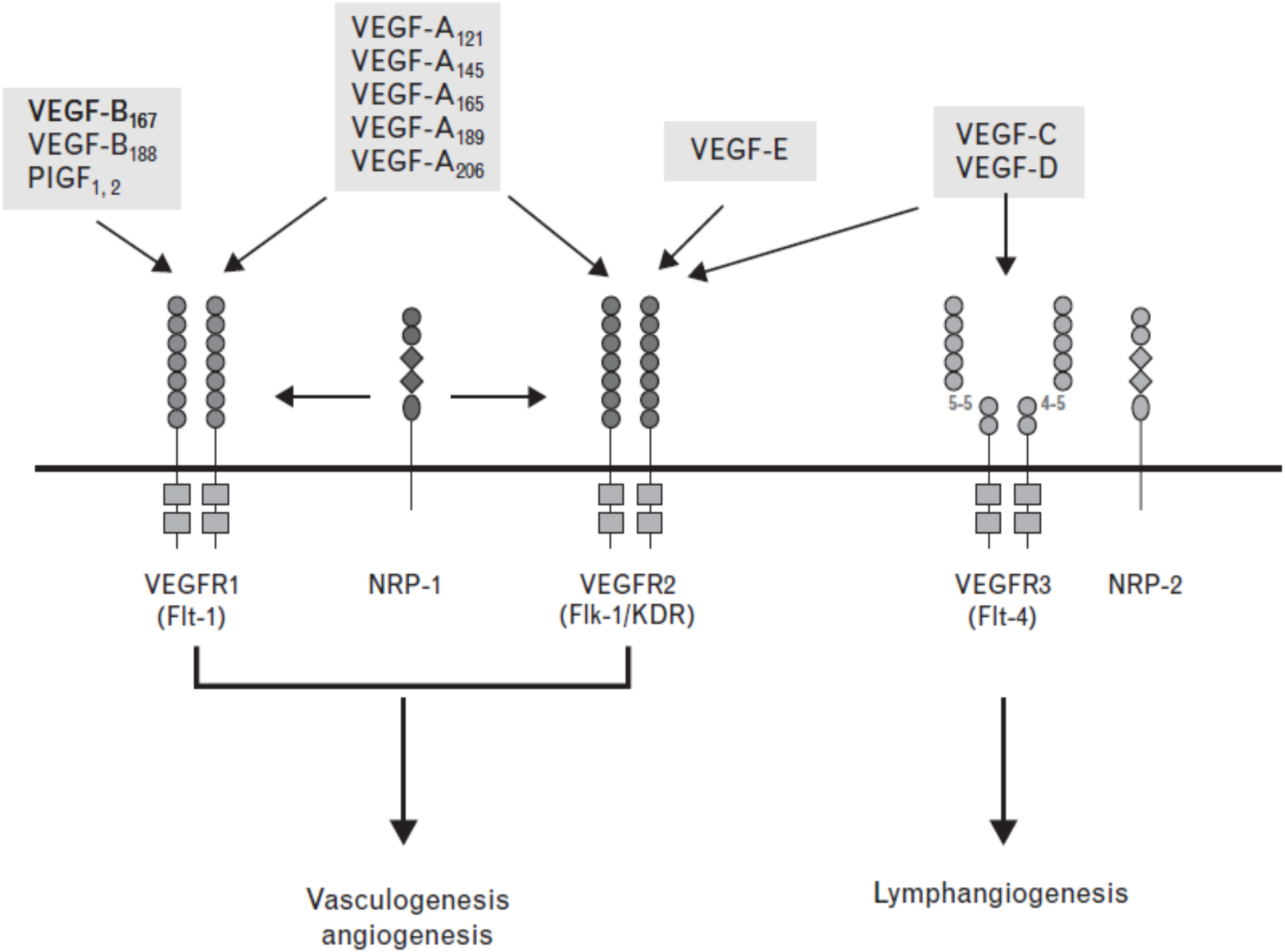

Drug development
Discovery
Pre-clinical
Phase I
Define safest dose, most effective delivery method and toxicity
Phase II
Efficacy in disease site under study
Phase III
Compare with standard treatment
Phase IV
Post-marketing surveillance
Biomarker development
Phase I
Preclinical exploratory studies: promising biomarkers identified
Phase II
Clinical assay and validation: development optimization and reproducibility of clinical assay
Phase III
Retrospective longitudinal: develop positive screening test and relationship between biomarker and clinical outcome
Phase IV
Prospective screening: determine operating characteristics of biomarker-based screening test
Phase V
Cancer control: estimate reductions in cancer mortality using screening test

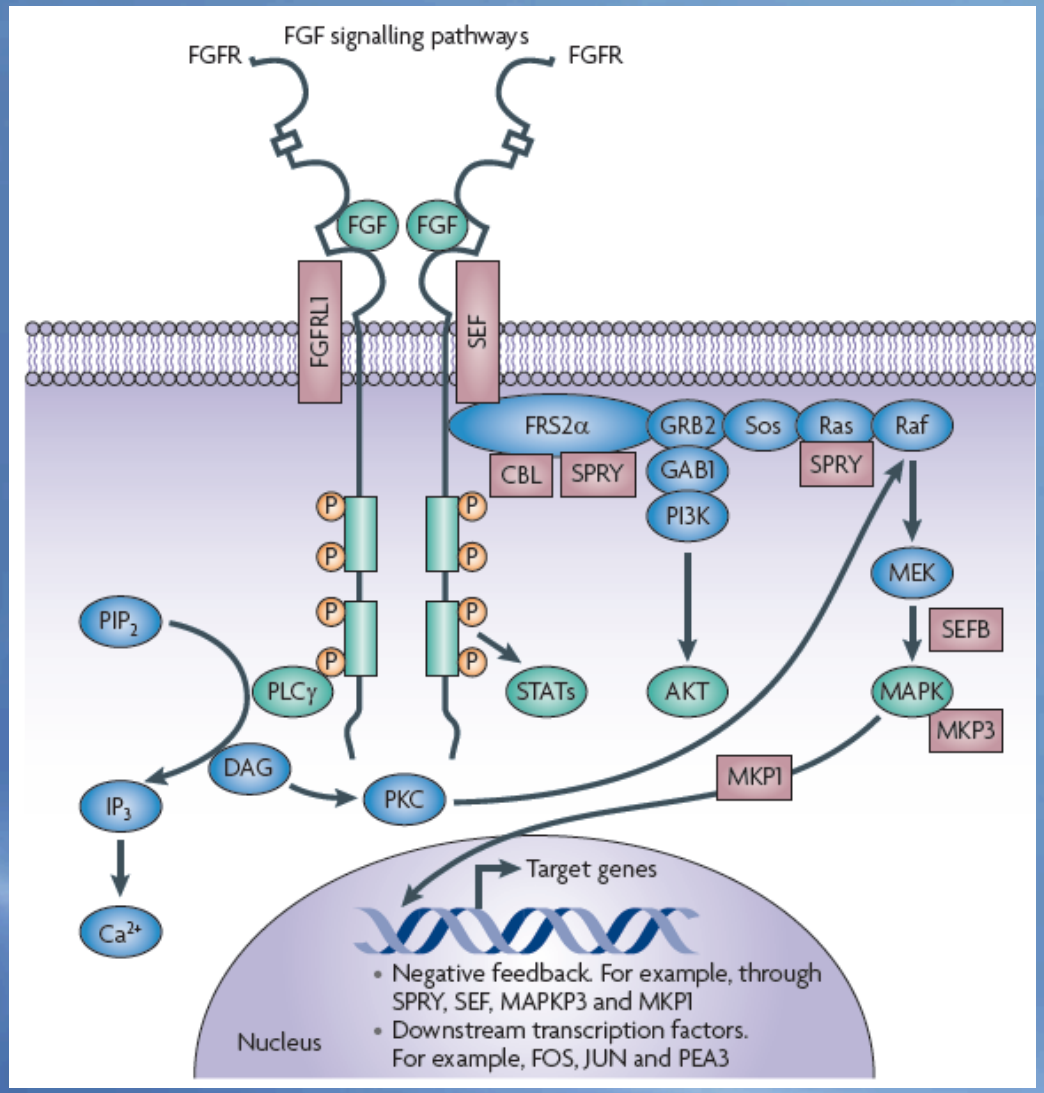


Name	EGFR/ErbB	c-KIT/ SCFR	VEGFR	HGFR/c-MET	RET
Main biological functions	Epithelial development, neuronal differentiation	Hematopoisis, mast cell development	Vascular development	Placenta, liver, muscle development	Kidney, neuronal diffrentiation
Mode of deregulation	Overexpression, deletions, point mutations	Deletions, point mutations	Deletions, point mutations	Overexpression, deletions, point mutations	Deletions, point mutations
Major malignancies	Breast, head and neck, glioblastoma moltiforma	Gastrointestinal stromal tumors, mastocytoma, acute myeloid leukemia	Vascularization of solid tumors	Renal, hepatocellular carcinoma	Multiple endocrine neoplasia, medullary thyroid carcinoma


VEGF-A121
VEGF-A145
VEGF-A165
VEGF-A189
VEGF-A206
VEGF-B167
VEGF-B188
PIGF1, 2
VEGF-E
VEGF-C
VEGF-D
5-5
4-5
VEGFR1
(Flt-1)
NRP-1
VEGFR2
(Flk-1/KDR)
VEGFR3
(Flt-4)
NRP-2
Vasculogenesis
angiogenesis
Lymphangiogenesis

FGF/FGFR network

- 18 ligands
- 4 TK receptors: FGFR1, FGFR2, FGFR3, FGFR4
- 1 non TK receptors: FGFRL1 (negative control)
- Regulatory activity of cell proliferation, survival, migration and angiogenesis



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Turner et al. Nat Canc Rev 2010

Tumor-specific genetic FGFR alterations

FGFR gene	Cancer type	Germline or somatic	Genetic changes	
FGFR1	Breast cancer	Somatic	Gene amplification	10%
	Ovarian cancer	Somatic	Gene amplification	5%
	Myeloproliferative syndrome	Somatic	Chromosomal translocation	
	Bladder cancer	Somatic	Gene amplification	3%
	Glioblastoma	Somatic	Missense mutation	
	Oral cancer	Somatic	Gene amplification	
	Melanoma	Somatic	Missense mutation	
	Rhabdomyosarcoma	Somatic	Gene amplification	3%
FGFR2	Breast cancer	Somatic	Gene amplification	
		Somatic	Missense mutation	
		Germline	Intronic regulatory SNPs	
	Gastric cancer	Somatic	Gene amplification	10%
		Somatic	Missense mutation	
	Lung cancer	Somatic	Missense mutation	
	Uterus cancer	Somatic	Missense mutation	12%
	Melanoma	Somatic	Missense mutation	
	Colorectal cancer	Somatic	Gene amplification	
FGFR3	Multiple myeloma	Somatic	Chromosomal translocation	
		Somatic	Missense mutation	
	Bladder cancer	Somatic	Missense mutation	10-60%
			Gene amplification	5%
	Cervical cancer	Somatic	Missense mutation	
	Colorectal cancer	Somatic	Missense mutation	
	Peripheral T-cell lymphoma	Somatic	Chromosomal translocation	
	Oral cancer	Somatic	Missense mutation	
	Testicular tumor	Somatic	Missense mutation	7%
FGFR4	Breast cancer	Germline	Missense coding SNP	
	Lung cancer	Germline	Missense coding SNP	
		Somatic	Missense mutation	
	Rhabdomyosarcoma	Somatic	Missense mutation	

FGFR: FGF receptor; SNP: Single-nucleotide polymorphism.

Katoh M, Expert Rev Antic Ther 2010

DEREGULATION of FGF SIGNALLING IN CANCER

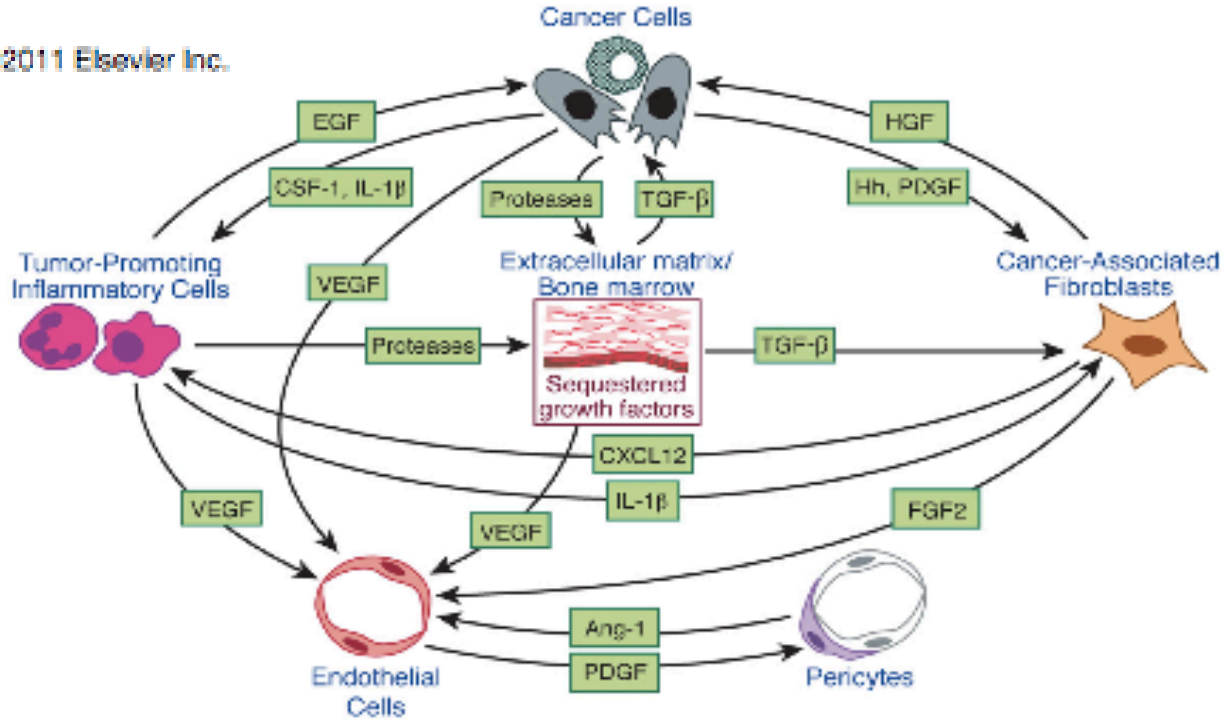
FGFR

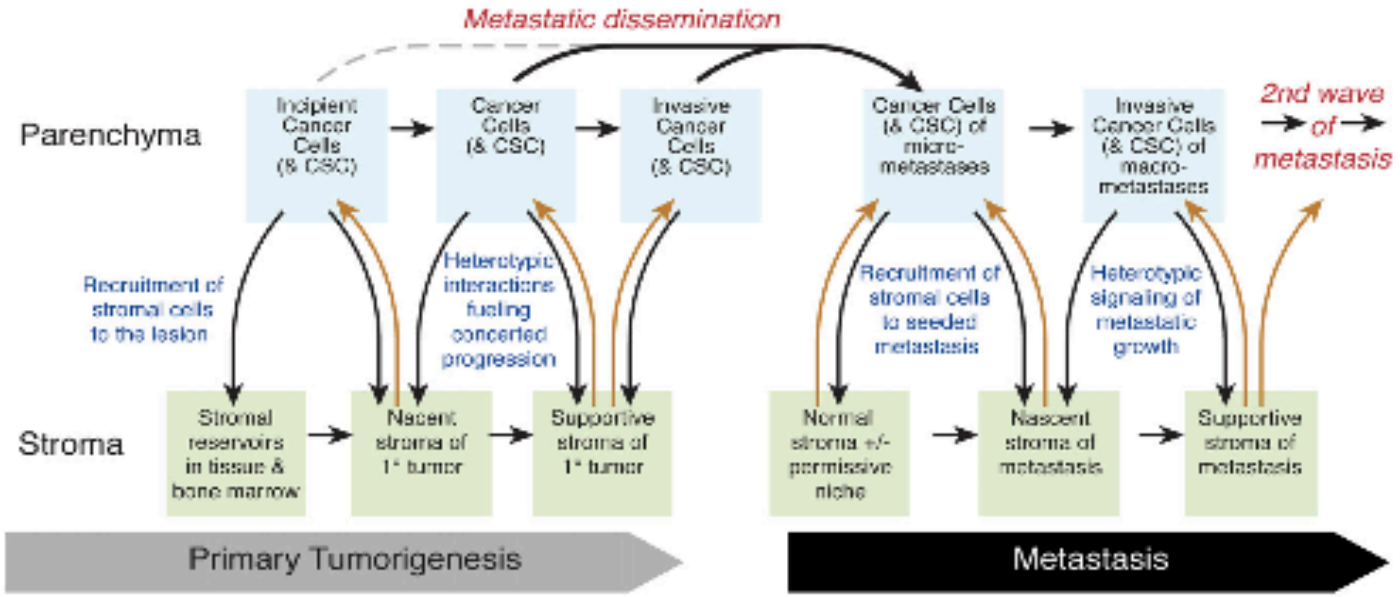
- ACTIVATING MUTATIONS
- GENE AMPLIFICATION
- CHROMOSOMAL TRASLOCATIONS

FGF

- AUTOCRINE SIGNALLING
- PARACRINE SIGNALLING

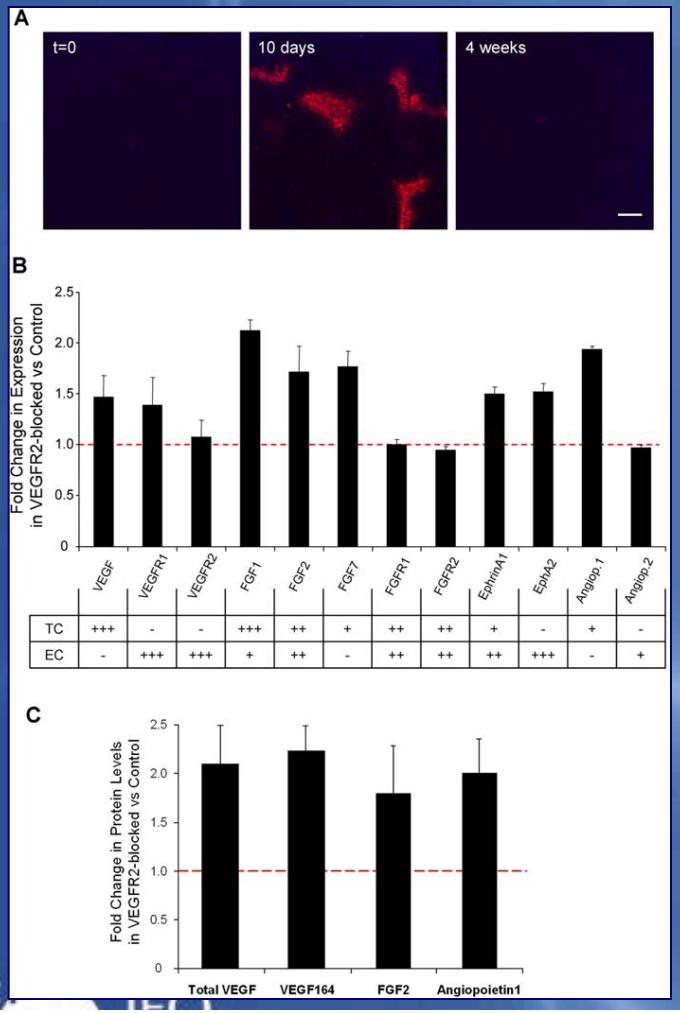
Cell 144, March 4, 2011 ©2011 Elsevier Inc.

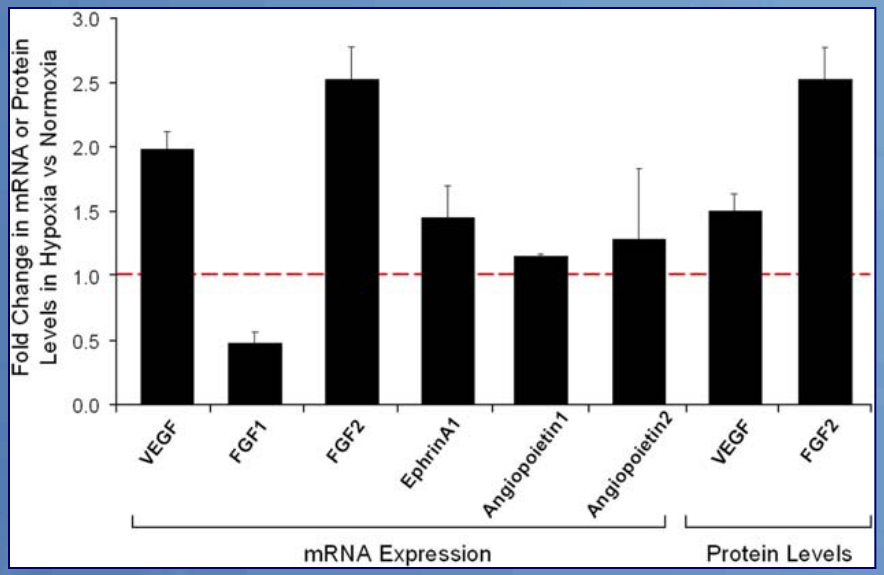




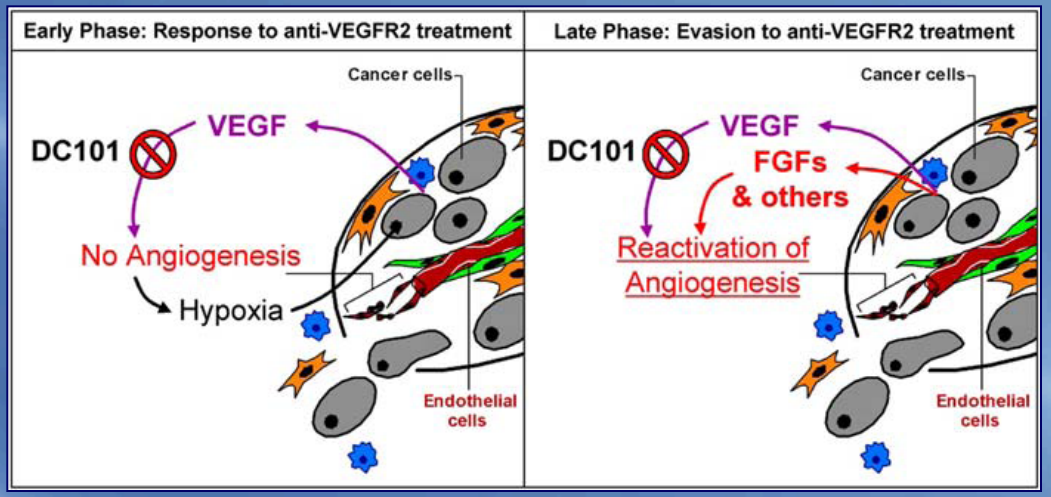
Evasion of antiangiogenic targeting of VEGF

1. VEGFR2 blockade →hypoxia →change of expression of proangiogenic factors in tumors





2. Hypoxia → ↑expression of proangiogenic factors in tumor-derived βTC cell line



Casanovas et al. Cancer Cell 2005

FGFR TKI

Agent	Company	Target	Clinical Development
Brivanib alaninate	BMS	VEGFR 1-2-3 FGFR 1-2-3	Phase III
Masitinib	AB Science	FGFR3, c-kit, PDGFR, FAK	Phase III (pancreas, GIST, multiple myeloma)
BIBIF1120	Boehringer Ingelheim	VEGFR 1-2-3 FGFR 1-2-3 PDGFR a & B	Phase III
TKI258 (Dovitinib)	Novartis	VEGFR 1-2-3, FLT, FGFR 3 cKit , PDGFR B	Phase II
TSU-68	Taiho Pharm.	VEGFR1, FGFR 1 PDGFR B	Phase I/II
E-3810	EOS	VEGFR ; FGFR1	Phase I
E7080	Eisai	FGFR, PDGFR, VEGFR	Phase I

FGFR TK inhibitors

	Sorafenib	Sutent	Brivanib	BIBF 1120	Dovitinib	E-3810
VEGFR1	-	2	350	34	10	7
VEGFR2	90	9	26	21	8	25
VEGFR3	20	17	10	13	27	10
FGFR1	-	-	150	69	Low	17.5
FGFR2	580	830	125	37	-	82.5
FGFR3	-	-	68	108	5	237.5
PDGFR	57	8	7,460	59/60	36	175/525
C-Kit	68	13	Low	-	2	456
Flt-3	58	10	58	-	1	-
Other	RET,RAF	RET	RET	Src	CSF-1R	CSF1R

Brivanib Single Agent Phase I Results

Phase I+Phase II AEs

Side Effects (grade I-III)	Frequency
Fatigue	33-45%
Anorexia	27-39%
Diarrohea	14-35%
Nausea	14-65%
Rash	6-24%
Hypertonia	9-28%
Emesis	9-41%

Dempke et al. Anticancer Res 2010

Phase I Antitumor Activity

Response[a]	All Doses, n (%)
Partial Response	2 (3)[b]
Stable Disease	24 (35)
Progressive Disease	32 (47)
Not assessable	10 (15)

[a] At least 1 post treatment CT;
[b] 1 Renal cell carcinoma 600 mg q1D; 1 Ampulla of Vater 1000 mg q1D

Jonker DJ et al. Annals Oncol 2010

Phase II Brivanib Single Agent in HCC

Dose: Brivanib 800 mg PO QD

Cohort A: no previous systemic CT for HCC

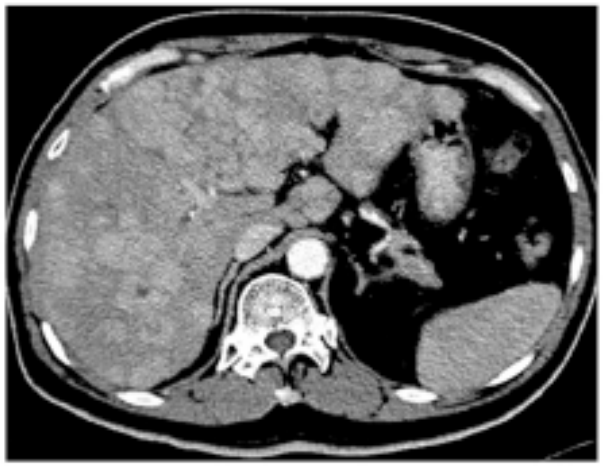
Cohort B: 1 prior regimen with antivascular therpies

End Points: PFS, TTP, OS, Disease control rate, Safety.

Baseline Characteristics	Cohort A (n=55)	Cohort B (n=46)
Age	60 (27-80)	55 (21-81)
Male/Female, %	89/11	72/28
Asian/non-Asian, %	64/36	67/33
HBV+/HCV-, %	53/22	65/17
ECOG PS 0/1/2, %	45/49/5	26/72/2
Extrahepatic spread, %	76	78
Child-Pugh A/B, %	91/9	91/9
AFP >UNL, %	76	83
Local Therapy (TACE, RFTA etc.), %	49	83

Park JW et al. Clin Cancer Res 2011

Brivanib induces responses in HCC pts



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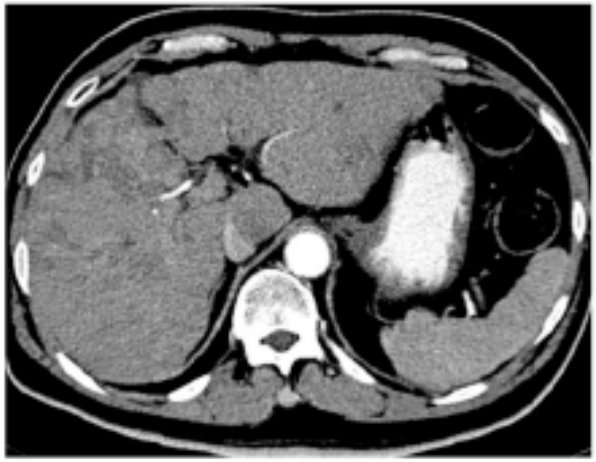
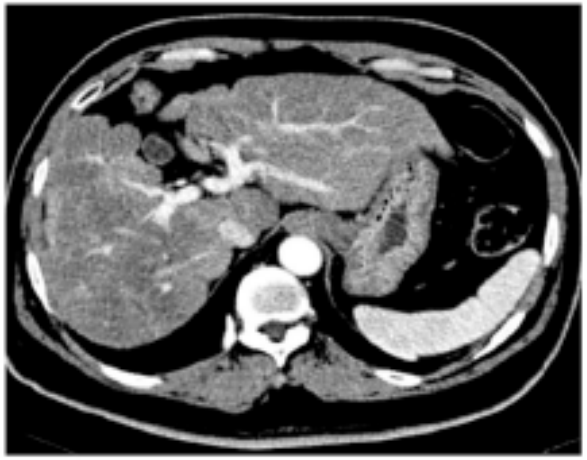
Baseline assessment



18 Mar 08

mWHO: SD
mRECIST: CR



12 May 09

mWHO: CR
mRECIST: CR

Park JW et al. Clin Cancer Res 2011

Tumor responses: mWHO and mRECIST

Outcome		
Overall Survival (95% CI) (median, months)	10 (95% CI, 6.8-15.2)	
	mWHO	**mRECIST**(3, 22)
Best tumor response, n (%)		
CR	1	5 (9.1)
PR	3 (5.5))	9 (16.4)
SD	24(43.6)	29 (52.7)
SD	22 (40.0)	
uCR	0	2 (3.6)
uPR	2 (3.6)	3 (5.5)
DCR (CR + PR + SD), n/N (%)	28/55 (50.9)	43/55 (78.2)
Median TTP(95% CI) (months)	2.8 (1.4–3.5)[a]	5.4 (2.8,–)
Median PFS (months)	2.7 (1.4-3.0)[a]	4.7 (2.8-5.7)
6-month PFS rate (%)	21.1 (9.6-32.5)[a]	35.6 (21.0-49.4)

[a]IRRC assessment

Park JW et al. Clin Cancer Res 2011

Future directions: Combo with Biologics

Phase I Trial of Brivanib + Cetuximab in GI tumors

Pts population: 60 pts with GI tumors relapsed after previous CTs (expansion cohort for CRC)

Doses:
Brivanib PO QD 250 → 800 mg D1-D8
Cetuximab 400 mg/m^2 C1D8 → 250 mg/m^2 qwk

G3/4 Aes: fatigue 16%, transaminitis 12%, diarrhoea 2%; 1 DLT: bilateral pulmonary emboli.

	Prior Therapy				
EGFR inhbitor	-	-	+	+	
VEGFR inhibitor	-	+	-	+	
Evaluable pts (total)	12	12	1	9	34
PR	4	1	0	0	5 (15%)
SD	5	7	1	6	19 (56%)
PD	3	4	0	3	10 (30%)
PR + SD ≥ 6 months	4	3	0	3	10 (30%)

Garrett CR et al. JCO 2008: abstr. 4111

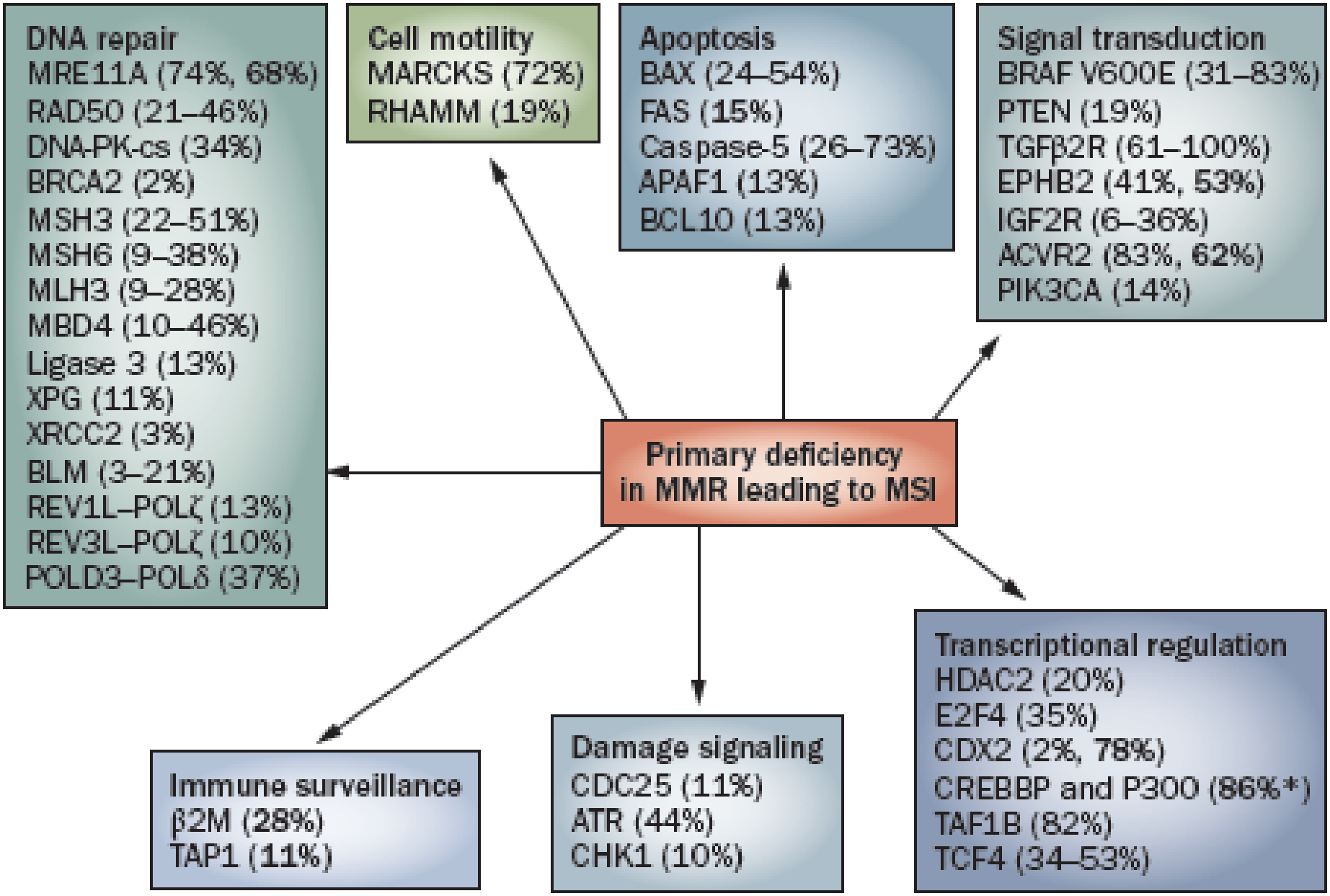
Mismatch repair deficient colorectal cancer in the era of personalized treatment

Madeleine Hewish, Christopher J. Lord, Sarah A. Martin, David Cunningham and Alan Ashworth

NATURE REVIEWS | CLINICAL ONCOLOGY

Key points

- Deficient MMR (dMMR) in colorectal cancer (CRC) occurs as a result of inherited or sporadic abnormalities
- Phenotypic characteristics, such as proximal anatomical location, mucinous features, lymphocytic infiltration, and pushing margins help to identify dMMR tumors
- The presence of dMMR in a tumor may be of relevance to the surgical management and systemic treatment of a patient
- Preclinical investigations suggest that cancer cells with dMMR show resistance to 5-fluorouracil, but are sensitive to irinotecan and mitomycin C; clinical data corroborate these findings although further studies are required
- Heterogeneity exists within the dMMR CRC subtype, which could be explained by the presence or absence of secondary mutations that occur as a consequence of the dMMR-associated mutator phenotype
- dMMR and the mutations that arise as a result of this deficiency could be exploited as novel therapeutic targets


DNA repair
MRE11A (74%, 68%)
RAD50 (21–46%)
DNA-PK-cs (34%)
BRCA2 (2%)
MSH3 (22–51%)
MSH6 (9–38%)
MLH3 (9–28%)
MBD4 (10–46%)
Ligase 3 (13%)
XPG (11%)
XRCC2 (3%)
BLM (3–21%)
REV1L–POLζ (13%)
REV3L–POLζ (10%)
POLD3–POLδ (37%)
Cell motility
MARCKS (72%)
RHAMM (19%)
Apoptosis
BAX (24–54%)
FAS (15%)
Caspase-5 (26–73%)
APAF1 (13%)
BCL10 (13%)
Signal transduction
BRAF V600E (31–83%)
PTEN (19%)
TGFβ2R (61–100%)
EPHB2 (41%, 53%)
IGF2R (6–36%)
ACVR2 (83%, 62%)
PIK3CA (14%)
Primary deficiency in MMR leading to MSI
Immune surveillance
β2M (28%)
TAP1 (11%)
Damage signaling
CDC25 (11%)
ATR (44%)
CHK1 (10%)
Transcriptional regulation
HDAC2 (20%)
E2F4 (35%)
CDX2 (2%, 78%)
CREBBP and P300 (86%*)
TAF1B (82%)
TCF4 (34–53%)

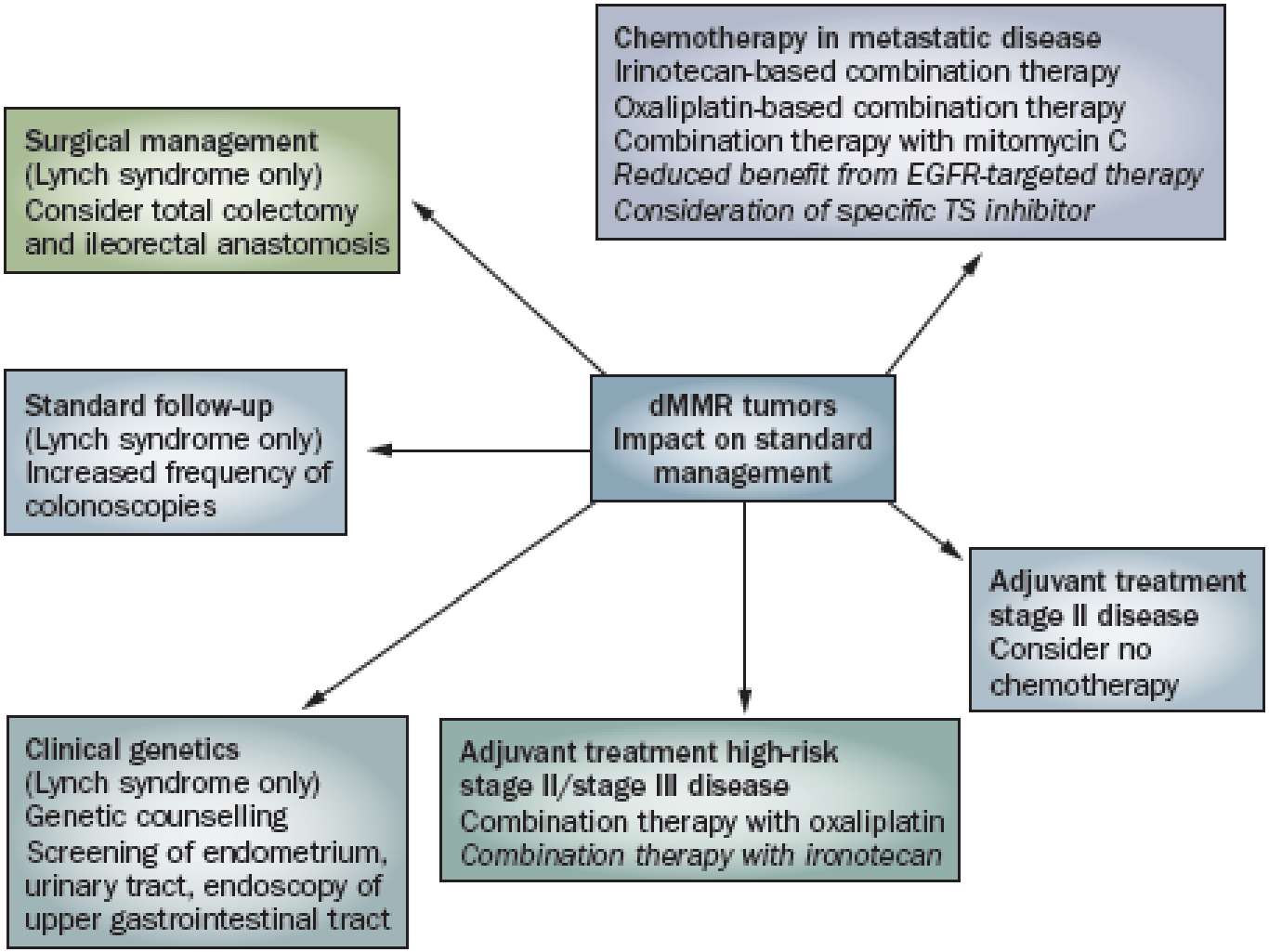


Figure 3 | The impact of dMMR on the management of colorectal cancer. The presence of dMMR in a tumor sample may affect many aspects of management. This includes screening, the systemic therapy given and patient follow-up. Recommendations for where there is a reasonable evidence-base are shown. Interpretations from *in vitro* data (in italics) require further examination in clinical studies. Abbreviations: dMMR, deficient mismatch repair; TS, thymidylate synthetase.

Table 3 | Trials assessing the effect of dMMR on 5-FU-based treatment outcomes

Reference	Tissue resource	Analyzed/ total	MSI frequency	Stage	Treatment	Result
Kim *et al.* (2007)[134]	NSABP trials between 1977 and 1990	542/ 5,555	18.1%	Dukes B & C	5-FU-based, portal or systemic vs no treatment	No predictive value of MSI
Jover *et al.* (2009)[135]	EPICOLON project	505/754	10.1%	Stage II & III	5-FU-based vs no treatment	Benefit of 5-FU restricted to pMMR alone (log rank P=0.00001 pMMR, P=0.7 dMMR)
Sargent *et al.* (2008)[66]	NCCTG, GIVIO, ECOG and data from Ribic *et al.*[136]	512 total	15%	Stage II & III	5-FU+levamisole, 5-FU+FO vs no treatment	Benefit of 5-FU restricted to pMMR alone (pMMR OS HR 0.69, P=0.047, dMMR OS HR 1.26, P=0.68). 5-FU treatment associated with inferior outcome in stage II disease HR 2.8, P=0.05
Tejpar *et al.* (2009)[137]	PETACC 3 trial	1,254/ 3,278	22% stage II 12% stage III	Stage II & III	5-FU+FO vs 5-FU +FO+irinotecan	Prognostic effect of MSI in patients treated with 5-FU (HR 0.05, P=0.0077)

Table 4 | Assessing the impact of dMMR on response to irinotecan

Reference	Trial	Analyzed/ total	MSI frequency	Disease stage	Treatment	Result
Fallik *et al.* (2003)[138]	Single trial	44/75	9.7%	Metastatic disease	Irinotecan	Improved response rate in MSI (P=0.009)
Charara *et al.* (2004)[139]	Single study rectal cancer	57	23%	Early stage disease	5-FU, irinotecan and radiotherapy	3/5 tumors with complete response were MSI, 10/36 with partial response
Tejpar *et al.* (2009)[137]	PETACC 3 trial	1254/3278	22% stage II 12% stage III	Stage II–III	5-FU+FO vs 5-FU+FO +irinotecan	No benefit for MSI patients when irinotecan added to 5-FU
Bertagnolli *et al.* (2009)[94]	CALGB 89803	723/1264	13.3%	Stage III	5-FU+FO vs weekly 5-FU+FO +irinotecan	dMMR patients receiving irinotecan had improved survival compared with pMMR (0.76, 95% CI 0.64–0.88 vs 0.59, 95% CI 0.53–0.64, P=0.03). No difference in 5-FU+FO treated patients

Abbreviations: CALGB, cancer and leukemia group B; dMMR, deficient mismatch repair; 5-FU, 5-fluorouracil; FO, folinic acid; MSI, microsatellite instability; PETACC, pan-European trials in adjuvant colon cancer; pMMR, proficient mismatch repair.

Metastatic Colo-Rectal Cancer

EGFR amplification/polisomy (FISH)

K-ras mutations
BRAF mutations
PIK3CA mutations
PTEN expression

TS expression
Defective mismatch repair DNA

ERCC1 expression

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The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2009.21.9170

JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Provisional Clinical Opinion: Testing for *KRAS* Gene Mutations in Patients With Metastatic Colorectal Carcinoma to Predict Response to Anti–Epidermal Growth Factor Receptor Monoclonal Antibody Therapy

Carmen J. Allegra, J. Milburn Jessup, Mark R. Somerfield, Stanley R. Hamilton, Elizabeth H. Hammond, Daniel F. Hayes, Pamela K. McAllister, Roscoe F. Morton, and Richard L. Schilsky

Provisional Clinical Opinion

Based on systematic reviews of the relevant literature, all patients with metastatic colorectal carcinoma who are candidates for anti-EGFR antibody therapy should have their tumor tested for* KRAS *mutations in a CLIA-accredited laboratory. If* KRAS *mutation in codon 12 or 13 is detected, then patients with metastatic colorectal carcinoma should not receive anti-EGFR antibody therapy as part of their treatment.

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Table 1 | Single arm studies with EGFR mAb therapies in metastatic CRC

Study	Treatment	*n*	*KRAS* wild type		*KRAS* mutant	
			n (%)	RR (%)	*n*	RR (%)
Moroni *et al.* (2005)[30]	Cetuximab Cetuximab + irinotecan Panitumumab	31	21 (67)	38	10 (32)	20
Lievre *et al.* (2008)[29]	Cetuximab Cetuximab + irinotecan Cetuximab + FOLFIRI	114	78 (68.4)	43.6	36 (31.6)	0
Freeman *et al.* (2008)[31]	Panitumumab	62	38 (61.3)	11	24 (38.7)	0
De Roock *et al.* (2008)[32]	Cetuximab Cetuximab + irinotecan	108	66 (61)	41	42 (39)	0
Khambada-Ford *et al.* (2007)[33]	Cetuximab	80	50 (62)	10	30 (38)	0
Benvenuti *et al.* (2007)[34]	Cetuximab Panitumumab Cetuximab + irinotecan	48	32 (67)	31	16 (33)	6
Frattini *et al.* (2007)[35]	Cetuximab + irinotecan Cetuximab + CAPOX	27	17 (63)	53	10 (37)	10
Di Fiore *et al.* (2007)[36]	Cetuximab + irinotecan Cetuximab + oxaliplatin	59	37 (63)	32	22 (37)	0
Finocchiaro *et al.* (2007)[37]	Cetuximab	81	49 (60)	26.5	32 (40)	6.3

Abbreviations: CAPOX, capecitabine and oxaliplatin; FOLFIRI, fluorouracil, folinic acid and irinotecan; RR, response rate.

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Table 2 | Randomized studies of EGFR mAb therapies in metastatic CRC

Study	Treatment	*n*	*KRAS* wild type*				*KRAS* mutant*			
			n (%)	RR (%)	PFS	OS (m)	*n* (%)	RR (%)	PFS	OS (m)
Monotherapy										
Amado *et al.* (2008)[39]	Panitumumab vs BSC	427	243 (57)	0 vs 17	7.3 vs 12.3w (HR 0.45)	7.6 vs 8.1 (HR 0.99)	184 (43)	0 vs 0	7.3 vs 7.4w (HR 0.99)	4.4 vs 4.9 (HR 1.02)
Karapetis *et al.* (2008)[40]	Cetuximab vs BSC	394	130 (58)	0 vs 13	1.9 vs 3.7m (HR 0.4; *P*<0.001)	4.8 vs 9.5 (HR 0.55; *P*<0.001)	164 (42)	0 vs 1	1.8 vs 1.8m (HR 0.99; *P*=0.96)	4.6 vs 4.5 (HR 0.98; *P*=0.89)
Combination therapy										
Van Cutsem *et al.* (2009)[42]	Cetuximab + FOLFIRI vs FOLFIRI	540†	348 (64)	43 vs 59	8.7 vs 9.9m (HR 0.68; *P*=0.02)	21 vs 24.9 (HR 0.84)	192 (36)	40 vs 36	8.1 vs 7.6m (HR 1.07; *P*=0.75)	17.7 vs 17.5 (HR 1.03)
Bokemeyer *et al.* (2009)[41]	Cetuximab + FOLFOX vs FOLFOX	233	134 (58)	37 vs 60	7.2 vs 7.7m (HR 0.57; *P*=0.163)	NA	99 (42)	49 vs 33	8.6 vs 5.5m (HR 1.830; *P*=0.0192)	NA
Siena *et al.* (2010)[44]	Panitumumab + FOLFOX vs FOLFOX	1,096	656 (60)	48 vs 55	8.0 vs 9.6m (HR 0.8; *P*=0.02)	19.7 vs 23.9 (HR 0.83; *P*=0.07)	440 (40)	40 vs 40	8.8 vs 7.3m (HR 1.29; *P*=0.02)	19.3 vs 15.5 (HR 1.24; *P*=0.07)
Peeters *et al.* (2010)[45]	Panitumumab + FOLFIRI vs FOLFIRI	1,083	597 (55)	10 vs 35	3.9 vs 5.9m (HR 0.73; *P*=0.004)	12.5 vs 14.5 (HR 0.85; *P*=0.12)	486 (45)	14 vs 13	4.9 vs 5.0m (HR 0.85; *P*=0.14)	11.1 vs 11.8 (HR 0.94; *P*=0.55)

*For all results presented in the table, results from the control arms are shown first before the experimental arm. †*KRAS* mutational analysis extended into 1,063 patients; *KRAS* wild type (*n*=666); PFS 8.4 months (C) versus 9.9 (Ab) months (HR=0.696; *P*=0.0012); OS 20.0 months (C) versus 23.5 months (Ab) (HR: 0.796; *P*=0.0093).[38] Abbreviations: BSC, best supportive care; m, months; NA, not applicable; RR, response rate; OS, overall survival; PFS, progression-free survival; w, weeks.

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CRYSTAL FOLFIRI ± Cetuximab N=1198 1st line	CO.17 Cetuximab vs BSC N=572 ≥ 2nd line	Panitumumab vs BSC Chemo-refractory N=463
Positive Primary Analysis		
• **PFS** prolonged • OAS no difference *VanCutsem NEJM '09*	• **OAS** prolonged • PFS prolonged *Jonker NEJM '07*	• **PFS** prolonged • OAS no difference (extensive cross-over) *VanCutsem JCO '07*
Analysis of efficacy by Kras		

• **Subgroup analysis** (not planned)
 	
• Kras
  • known: 49% pts
  • mutated: 36% pts
• WT:
  • HR PFS 0.68 p=0.017
• Mut:
  • HR PFS **1.07** p=0.75
 	
• **Interaction** test:: 0.07
 	
VanCutsem NEJM '09
	• **Subgroup analysis** (late-planned with blinded data)
	
	• Kras
	  • known: 69% pts
	  • mutated: 41% pts
	• WT:
	  • HR OAS 0.55 p<0.001
	• Mut:
	  • HR OAS **0.98** p=0.89
	
	• **Interaction** test: **p=0.01**
	
	Karapetis NEJM '08
		• **Subgroup analysis** (late-planned with blinded data)
		
		• Kras
		  • known: 92% pts
		  • mutated: 43% pts
		• WT:
		  • HR PFS 0.45
		• Mut:
		  • HR PFS **0.99**
		
		• **Interaction** test: **p<0.0001**
		
		Amado JCO '08

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OPUS	EPIC	CAIRO-2	PACCE
FOLFOX ± Cetuximab **N=337 1st line**	**Irinotecan± Cetuximab** **N=1298 2nd line**	**CT+beva ± Cetuximab** **N=755 1st line**	**CT+beva ± Cetuximab** **N=1053 1st line**
Negative Primary Analysis			
• **RR** +10% p=0.06 • PFS no difference • OAS nr *Bokemeyer JCO '09*	• **OAS** no difference • PFS prolonged *Sobrero, JCO 08*	• **PFS** worse • OAS no difference *Tol, NEJM '09*	• **PFS** worse • OAS worse *Hecht , JCO 08*
Analysis of efficacy by Kras			

• **Subgroup analysis** (not planned)
• Kras
  • known: 69% pts
  • mutated: 42% pts
• WT:
  • OR resp=**2.5**, p=0.011
  • HR PFS **0.57** p=0.016
• Mut:
  • OR resp=**0.5**, p=0.11
  • HR PFS **1.83** p=0.019
• **Interaction** test:
  • Response **0.003**
  • PFS: **0.0007**
Bokemeyer JCO '09
	• **Subgroup analysis** (not planned)
	• Kras
	  • known: 23% pts (US)
	  • mutated: 36% pts
	• WT:
	  • HR OAS 1.29 p=0.18
	• Mut:
	  • HR OAS 1.28 p=0.29
	• **Interaction** test: **0.989**
	ImClone at FDA '08
		• **Subgroup analysis** (anticipated, not planned)
		• Kras
		  • known: 70% pts
		  • mutated: 40% pts
		• WT:
		  • PFS no diff p=0.30
		• Mut:
		  • PFS worse p=0.003
		• **Interaction** test: **nr**
		Tol, NEJM '09
			• **Subgroup analysis** (exploratory, not planned)
			• Kras (Oxal cohort)
			  • known: 81% pts
			  • mutated: 40% pts
			• WT:
			  • HR PFS 1.36 p<0.05
			• Mut:
			  • HR PFS 1.25 p ns
			• **Interaction** test: **nr**
			Hecht , JCO 08

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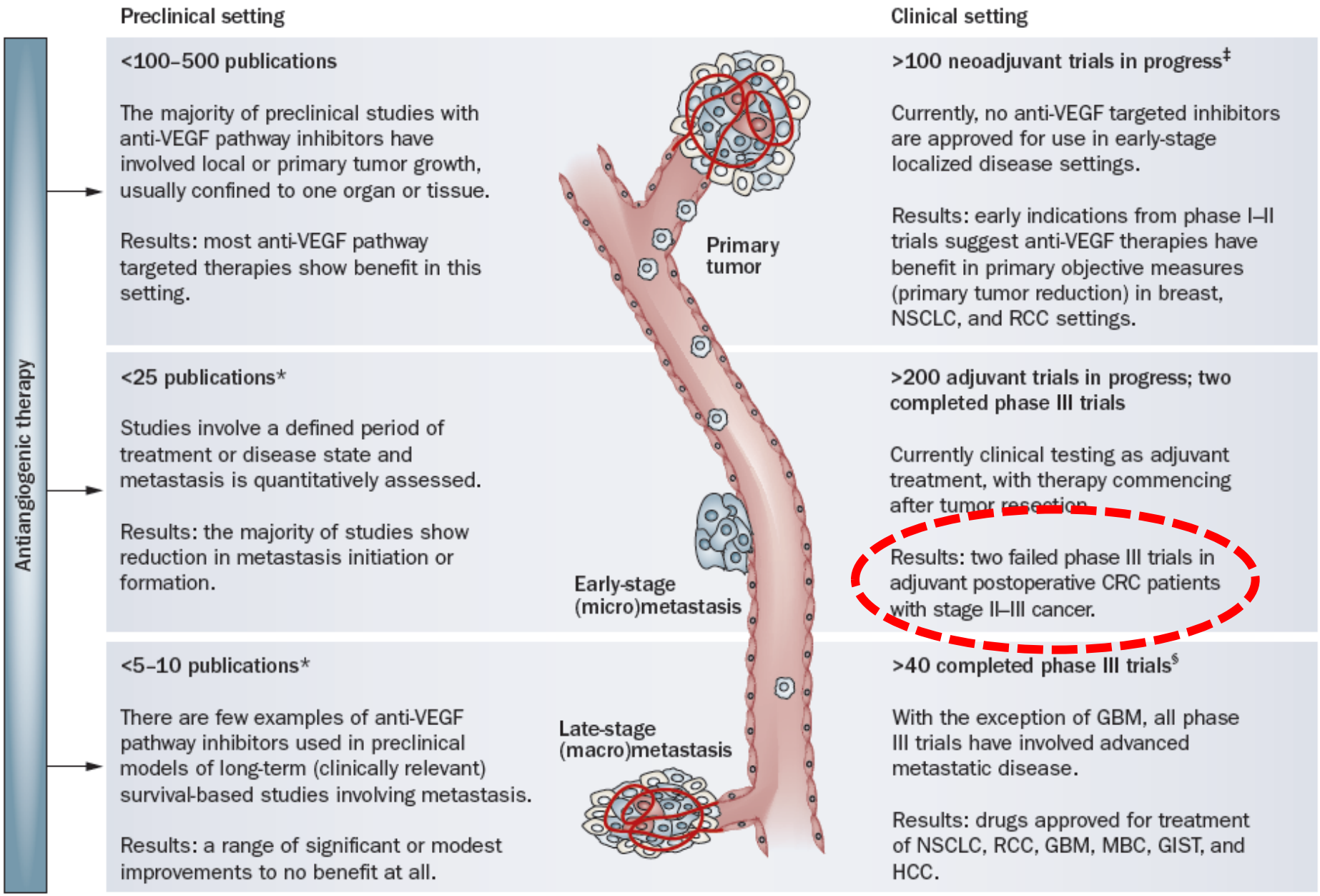

Antiangiogenic therapy: impact on invasion, disease progression, and metastasis

John M. L. Ebos and Robert S. Kerbel

Istituto Europeo di Oncologia

Nature Rew Clin Oncol Ap

Antiangiogenic therapy: impact on invasion, disease progression, and metastasis

John M. L. Ebos and Robert S. Kerbel

NATURE REVIEWS | CLINICAL ONCOLOGY VOLUME 8 | APRIL 2011 |

Table 1 | Successful completed phase III trials with anti-VEGF pathway agents

Combined with	Tumor (setting)	↑ PFS?	↑ OS?	Trial identifier
Bevacizumab				
FOLFIRI	CRC (1st)	Yes	Yes*	AVF2107[96]
FOLFOX or XELOX	CRC (1st)	Yes*	Yes	NO16966[15]
FOLFOX	CRC (2nd)	Yes	Yes*	E3200[97]

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Table 2 | Unsuccessful or terminated phase III trials with anti-VEGF pathway agents

Combined with	Tumor (setting)	↑ PFS?	↑ OS?	Identifier
Bevacizumab				
XELOX and cetuximab	CRC (1st)	No*‡	NA	PACCE[115]
Oxaliplatin or irinotecan and panitumumab	CRC (1st)	No*‡	NA	CAIRO2[116]
FOLFOX	CRC (adjuvant)	No§	NA	NSABP-C-08[89]
PTK787				
FOLFOX	CRC (2nd)	Yes	No*	CONFIRM 2[126]
FOLFOX	CRC (1st)	No	No*	CONFIRM 1‖
Semaxanib				
FOLFIRI	CRC (1st)	NA	No*	NCT00021281‖
Leucovorin and 5-FU	CRC (1st)	NA	No*	NCT00004252‖
Sunitinib				
FOLFIRI	CRC (1st)	No*	NA	SUN 1122‖
Cediranib				
FOLFOX	CRC (1st)	Yes	No*	HORIZON III‖

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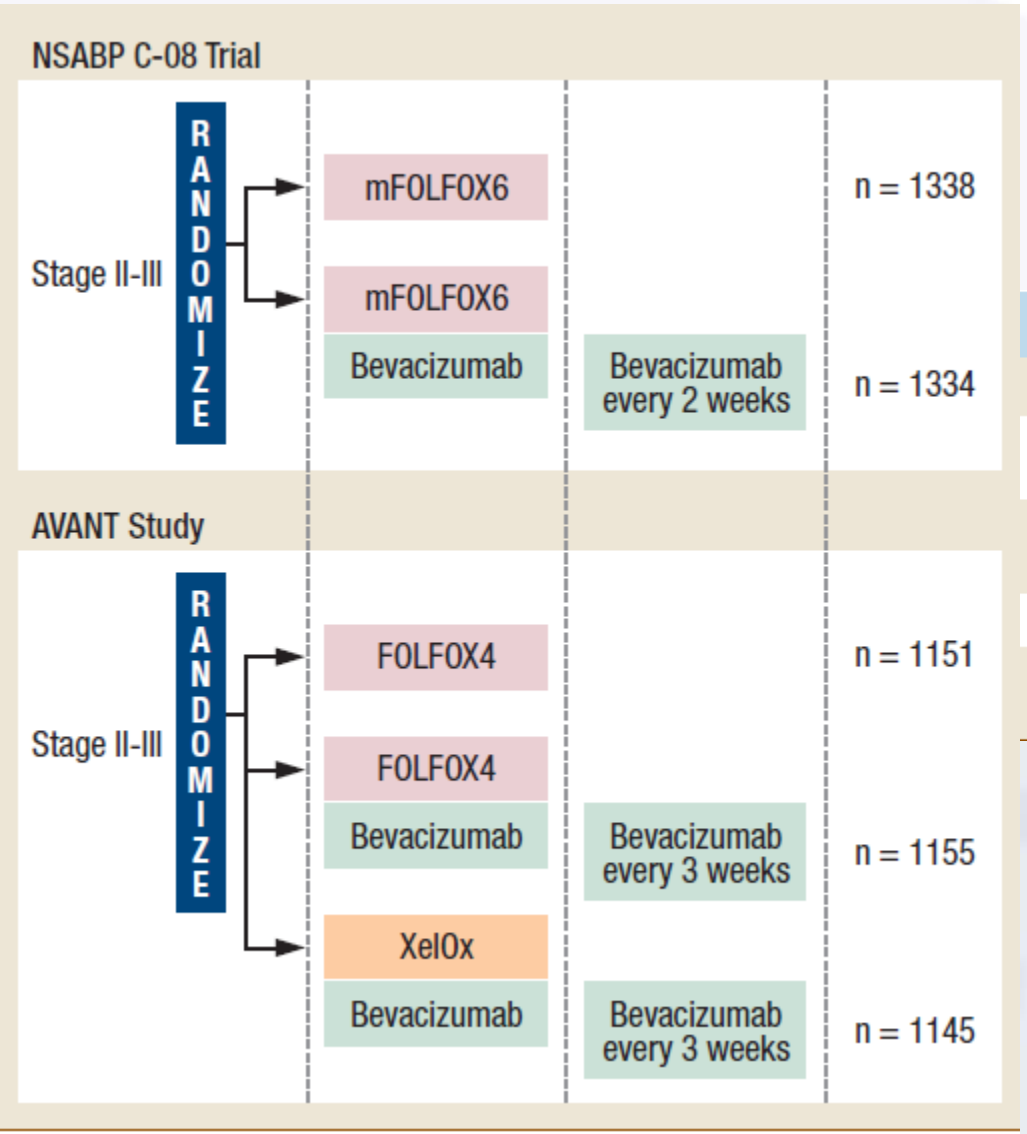


Variable	NSABP C-08	AVANT
Number of Arms	2	3
Chemotherapy Regimen	mFOLFOX6	FOLFOX4, XelOx
Maintenance Bevacizumab	5 mg/kg every 2 weeks	7.5 mg/kg every 3 weeks
Analysis	Stage II and III	Stage III only
Participating Centers	United States	Multinational

Clinical Colorectal Cancer December 2010

Variable	NSABP C-08	AVANT
Number of Arms	2	3
Chemotherapy Regimen	mFOLFOX6	FOLFOX4, XelOx
Maintenance Bevacizumab	5 mg/kg every 2 weeks	7.5 mg/kg every 3 weeks
Analysis	Stage II and III	Stage III only
Participating Centers	United States	Multinational

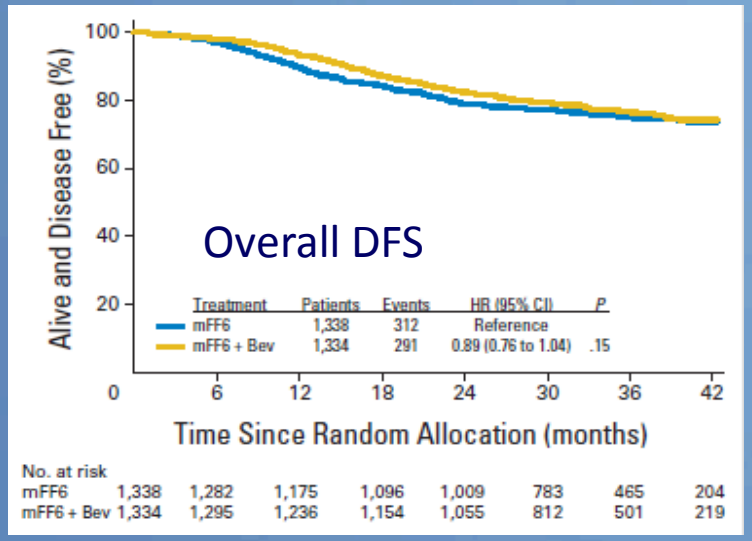
Adverse Event	Oxaliplatin-Based CT (n = 2447)	Oxaliplatin-Based CT + Bevacizumab (n = 3606)	*P* Value
	Number of Patients (%)	Number of Patients (%)	
Venous Thrombosis	123 (5)	231 (6.4)	.0286[a]
Arterial Thrombotic Events	30 (1.2)	60 (1.7)	.2029
GI Perforation	4 (0.2)	14 (0.4)	.1817
Hemorrhage	32 (1.3)	44 (1.2)	.8552
Hypertension	36 (1.5)	387 (10.7)	< .0001[a]
Proteinuria	12 (0.5)	58 (1.6)	.0001[a]
Wound Complications	8 (0.3)	31 (0.9)	.0174[a]

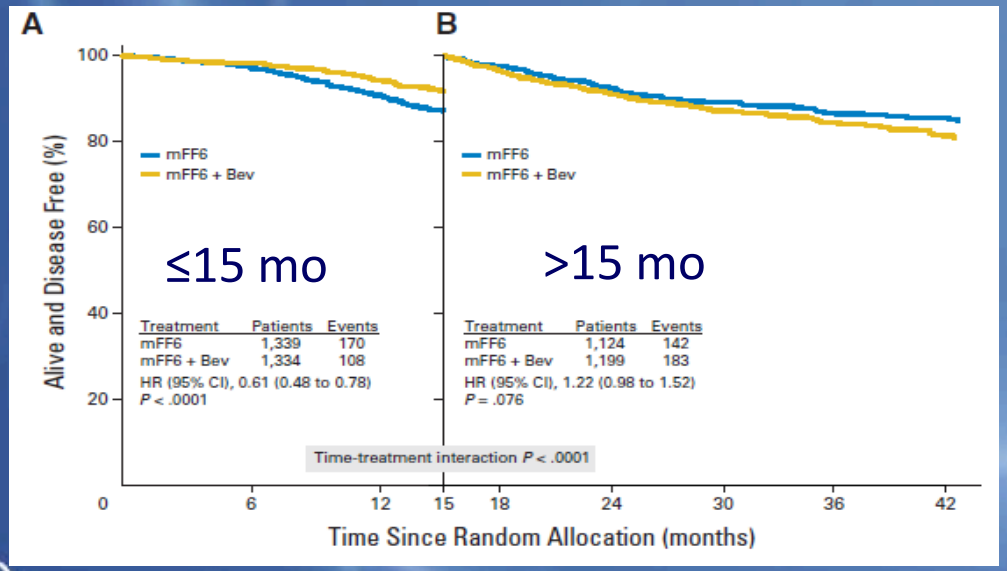
NSABP C-08 trial

Schedule: mFOLFO6 ± Bev q2wks

Patients 2672 with stage II and III CRC
(1354 with Bev; 1356 withouth Bev)

Primary End Point: DFS





NEGATIVE BUT…

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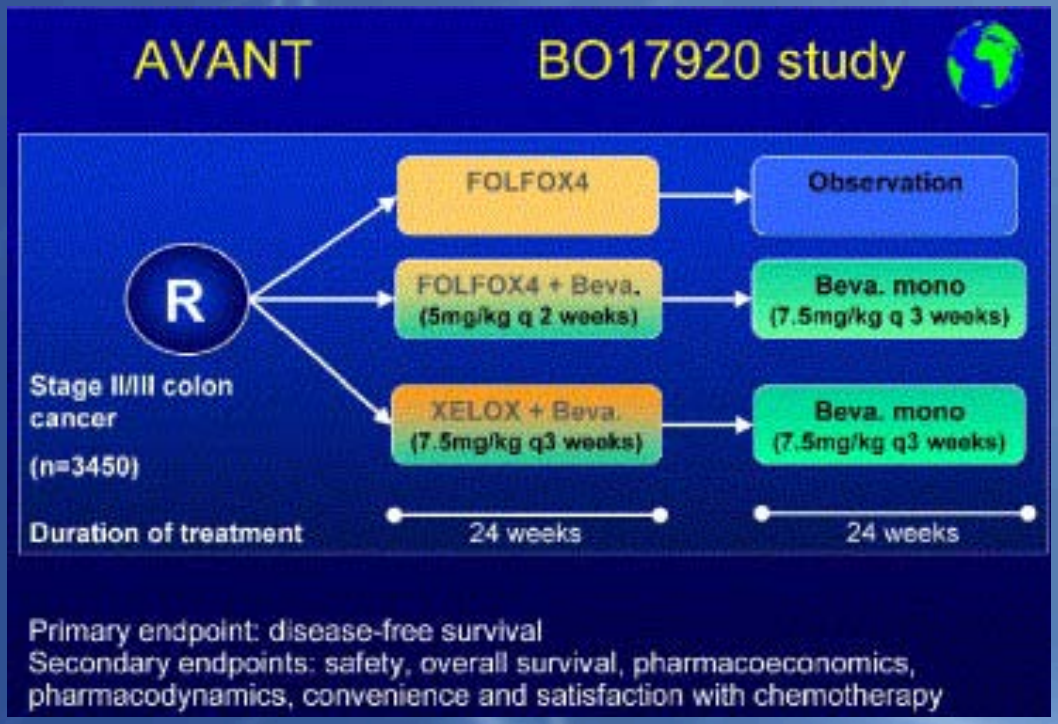
Allegra et al, JCO 2011

Bevacizumab in adiuvant setting for CRC: AVANT trial



Patients 3451 with stage II and III CRC

RESULTS:
Primary End Point DFS:
FAILED

Secondary END Point OS:
FAILED

Efficacy results in favor CT alone → more relapses and deaths in Bev arms

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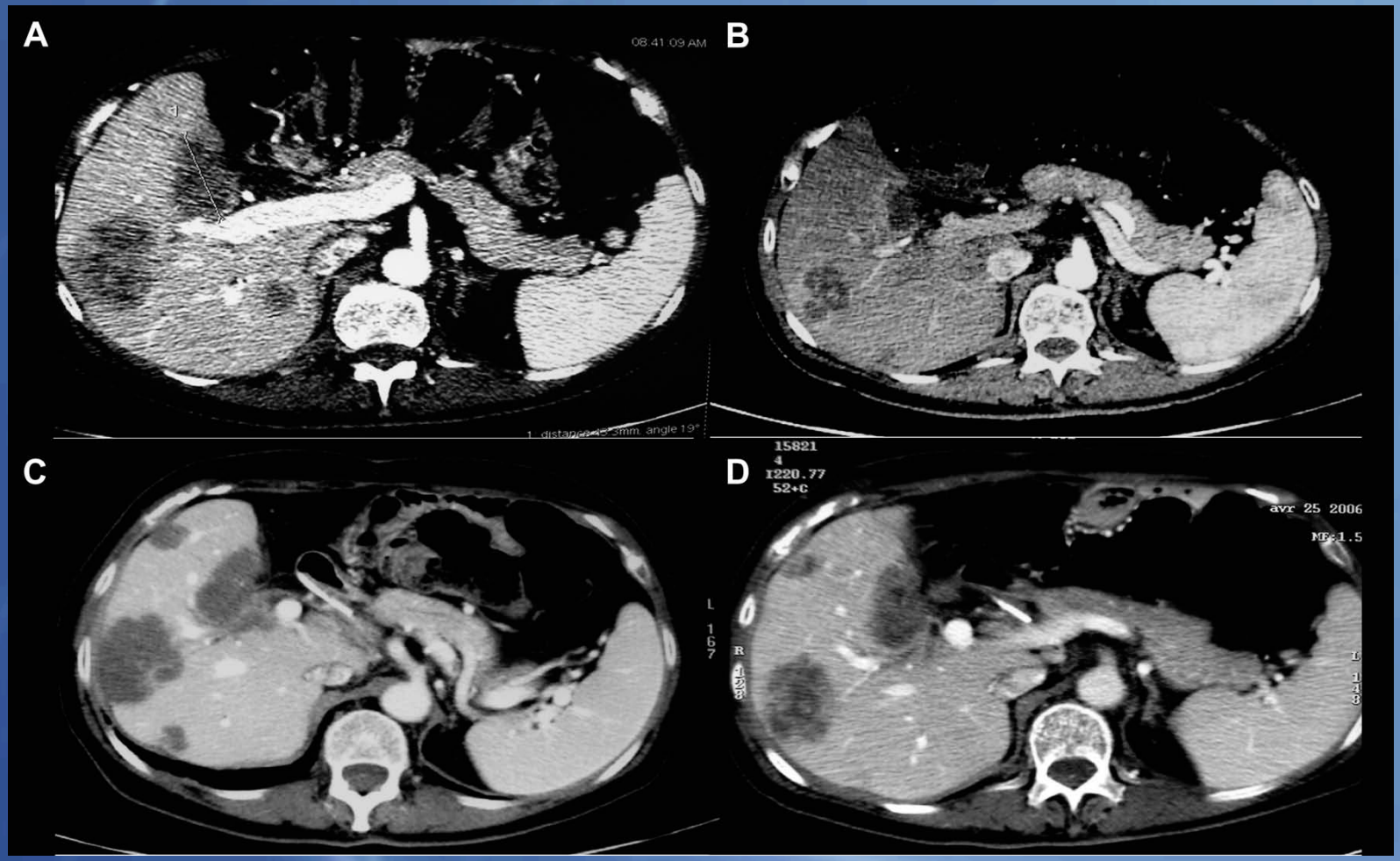
De Gramont et al, Seminars in Oncol 2006

Rebound after Bev cessation



(A) before first Bev treatment, (B) during first Bev treatment, before surgery, (C) 1 mo after colon and liver surgery and (D) during second BV treatment, after surgery.

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Cacheux W et al. Ann Oncol 2008;19:1659-1661

VOLUME 28 · NUMBER 20 · JULY 10 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Defective Mismatch Repair As a Predictive Marker for Lack of Efficacy of Fluorouracil-Based Adjuvant Therapy in Colon Cancer

Daniel J. Sargent, Silvia Marsoni, Genevieve Monges, Stephen N. Thibodeau, Roberto Labianca, Stanley R. Hamilton, Amy J. French, Brian Kabat, Nathan R. Foster, Valter Torri, Christine Ribic, Axel Grothey, Malcolm Moore, Alberto Zaniboni, Jean-Francois Seitz, Frank Sinicrope, and Steven Gallinger

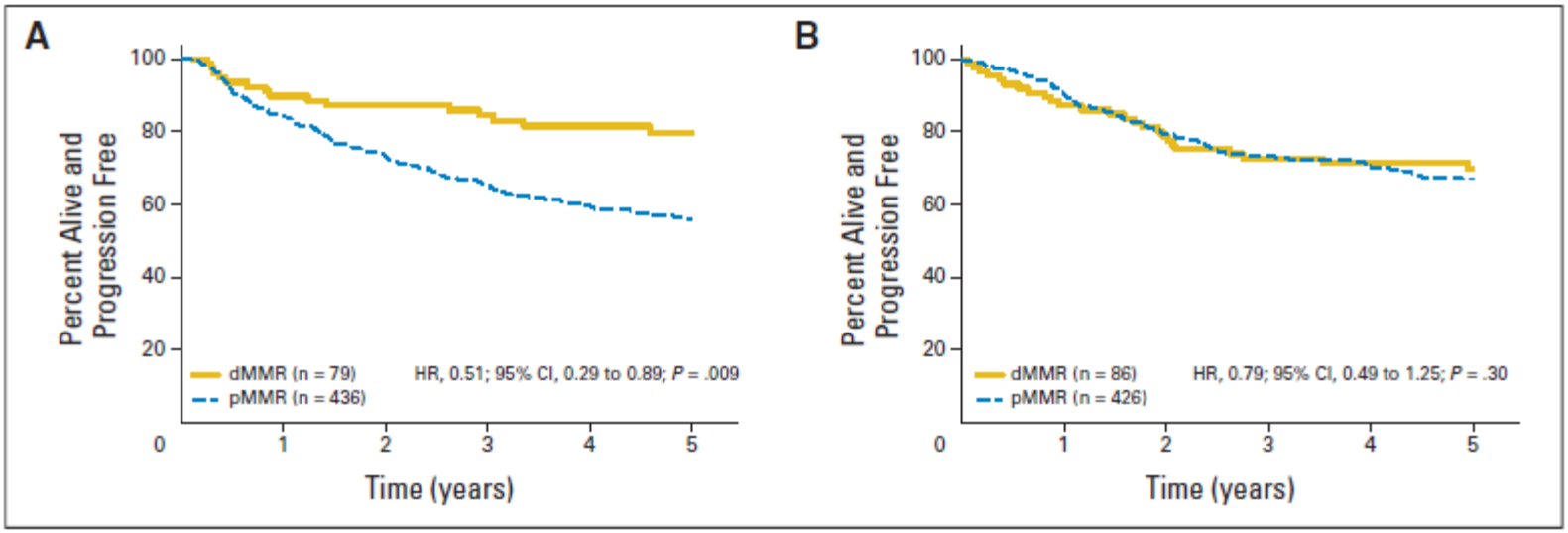

Fig 1. (A) Disease-free survival (DFS) in untreated patients by DNA mismatch repair (MMR) status. (B) DFS in treated patients by MMR. dMMR, defective DNA mismatch repair; pMMR, proficient DNA mismatch repair.

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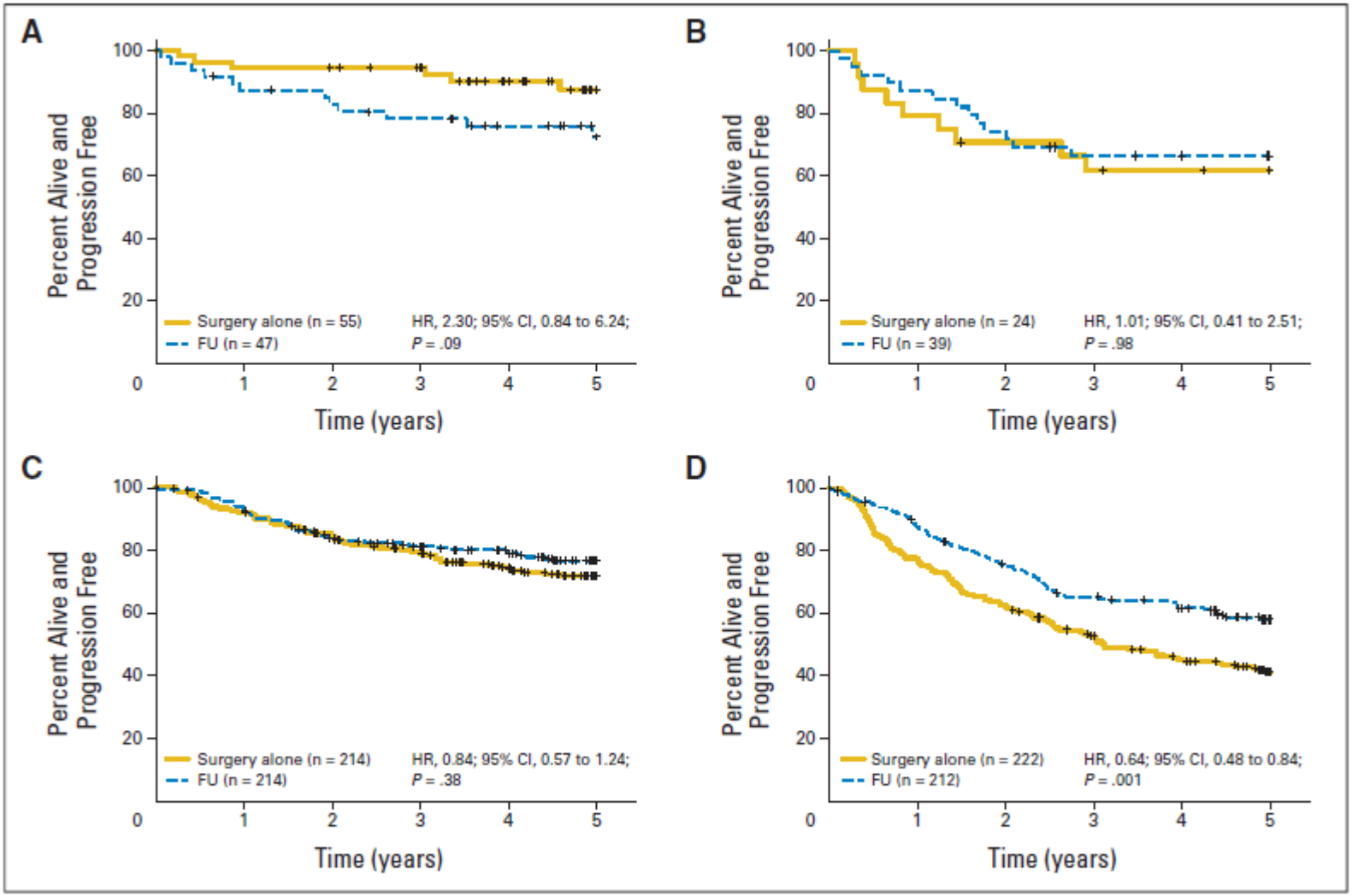

Fig 2. (A) Disease-free survival (DFS) in patients with stage II disease and defective DNA mismatch repair (dMMR) by treatment status. (B) DFS in patients with stage III disease and dMMR by treatment status. (C) DFS in patients with stage II disease and proficient MMR (pMMR) by treatment status. (D) DFS in patients with stage III disease and pMMR by treatment status. HR, hazard ratio; FU, fluorouracil.

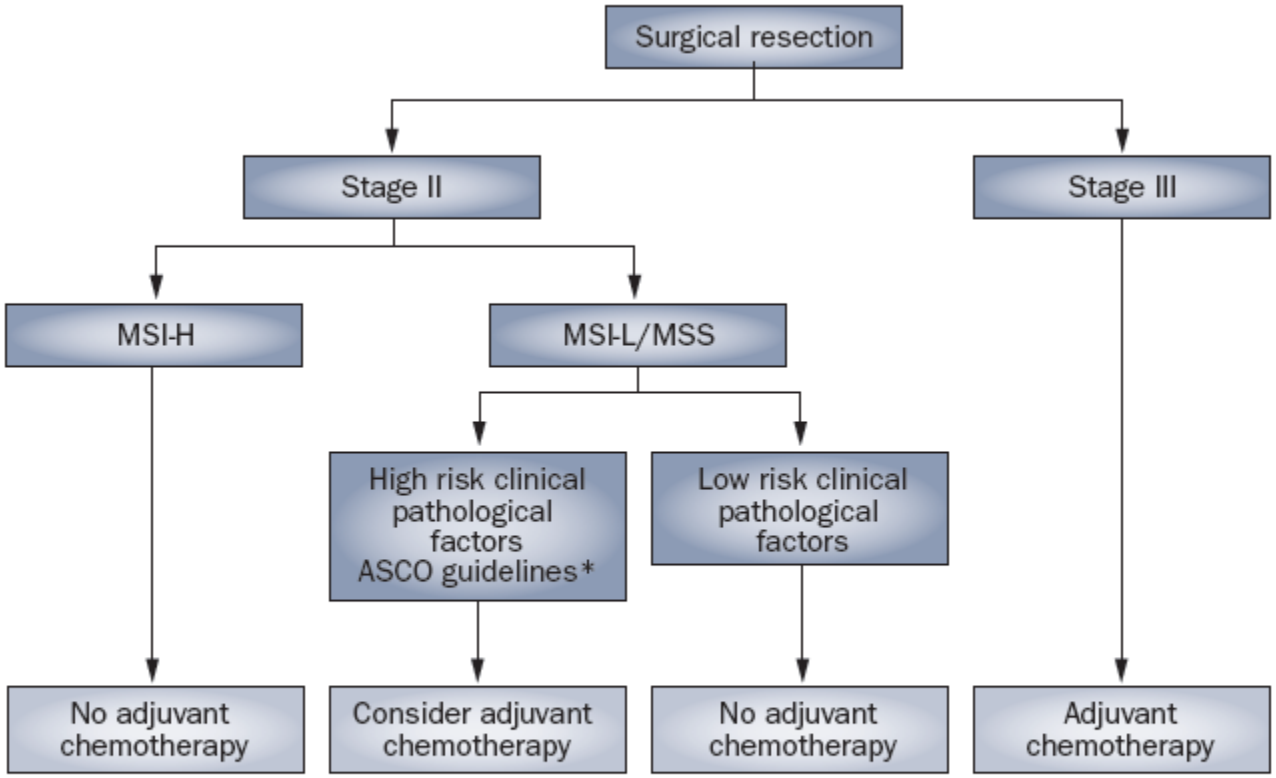

Figure 1 | Proposed algorithm colorectal cancer. Algorithm for utilizing microsatellite instability (MSI) alongside clinical pathological factors in stage II and III colorectal cancer.

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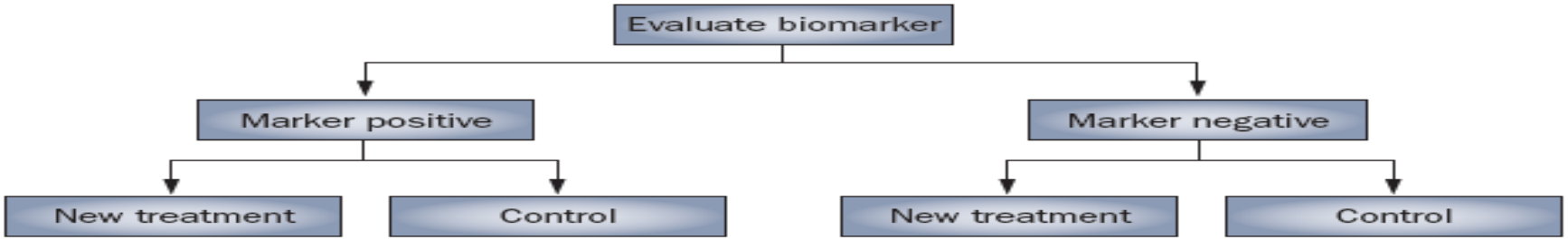


Figure 4 | Biomarker stratified design. There is not a sufficient basis for using the biomarker to restrict eligibility so both the 'marker positive' and 'marker negative' groups are randomized between the new treatment and control. For these designs it is crucial to state a prospective analysis plan that defines how the biomarker result will be used in the analysis.

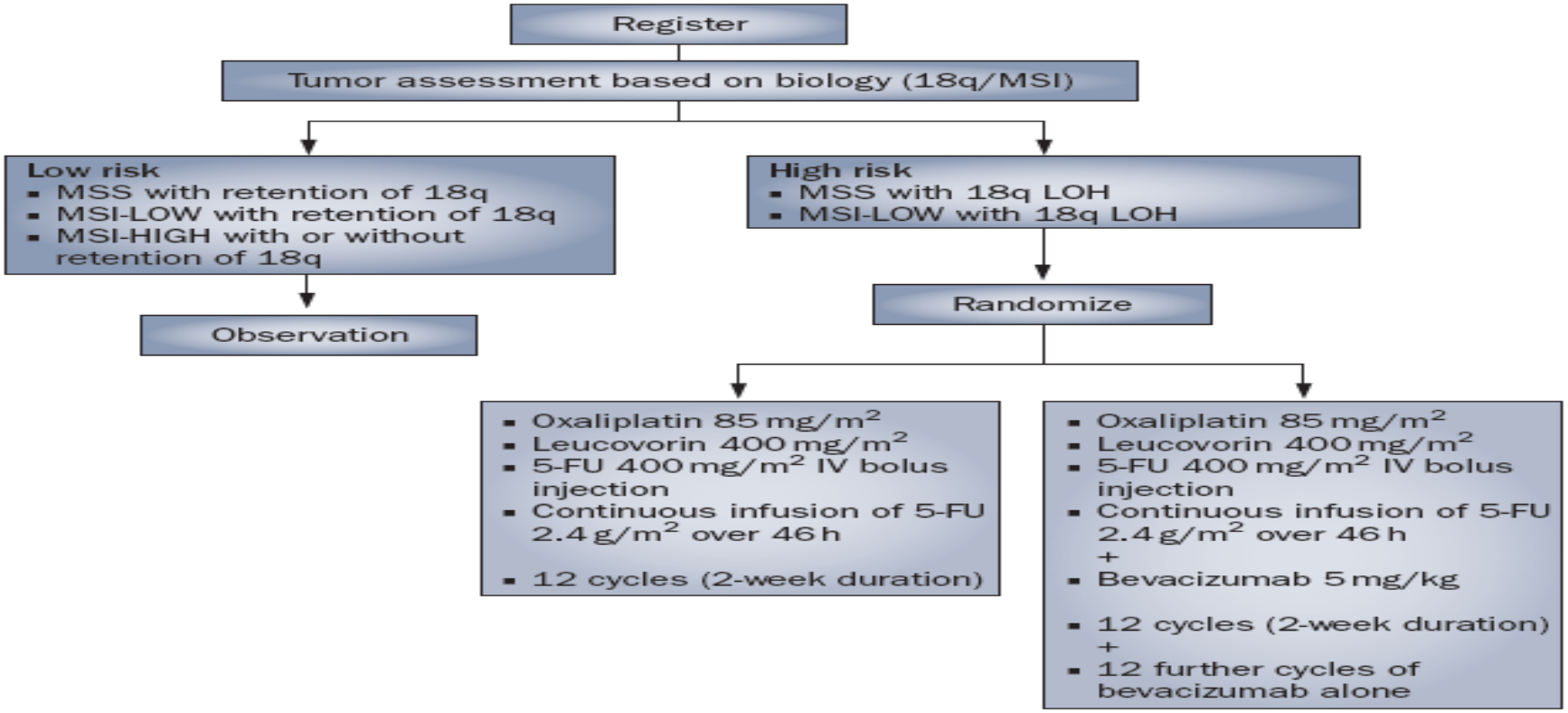
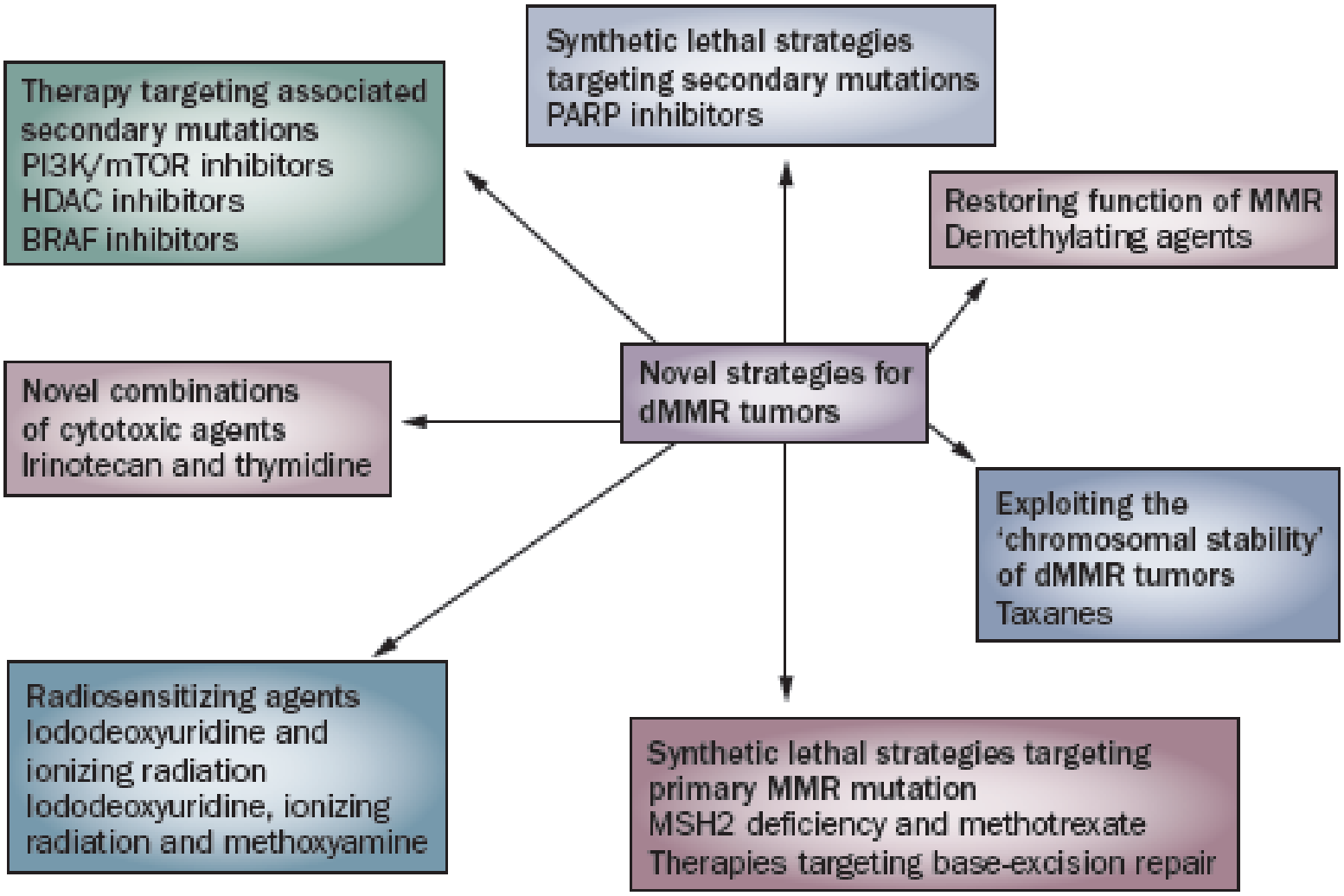


Figure 5 | Hybrid biomarker design. Eastern Cooperative Oncology Group E5202 study design for stage II colorectal cancer. Only patients defined by presence of the marker are randomized to the control or treatment arms.


Therapy targeting associated secondary mutations
PI3K/mTOR inhibitors
HDAC inhibitors
BRAF inhibitors
Synthetic lethal strategies targeting secondary mutations
PARP inhibitors
Restoring function of MMR
Demethylating agents
Novel combinations of cytotoxic agents
Irinotecan and thymidine
Novel strategies for dMMR tumors
Exploiting the 'chromosomal stability' of dMMR tumors
Taxanes
Radiosensitizing agents
Iododeoxyuridine and ionizing radiation
Iododeoxyuridine, ionizing radiation and methoxyamine
Synthetic lethal strategies targeting primary MMR mutation
MSH2 deficiency and methotrexate
Therapies targeting base-excision repair

Review

Expert Opinion

New targeted therapies for gastric cancer

Yoshinari Asaoka[†], Tsuneo Ikenoue & Kazuhiko Koike

Istituto Europeo di Oncologia

Sample name	Histology	ErbB2	c-Met	FGFR2	PIK3CA	KRAS	APC	CTNNB1
AGS	Well				E453K	G12D		G34E
ECC10	Small cell						T1556fs*3	
ECC12	Small cell							
GCIY	Poorly							
KATOIII	Poorly			Amp				
MKN1	Adenosquamous				E545K	Amp		
MKN45	Poorly		Amp					
MKN7	Well	Amp						
NCI-N87	Well	Amp						
SNU-1	Poorly					G12D		
SNU-16	Poorly			Amp				
SNU-5	Poorly		Amp					
NUGC-3	Poorly							
TGBC11TKB	Well				E545D	G12D	G1106fs*20 T1556fs*3	

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Molecular target	Agents	Target	Approval/trials	Trials targeting gastric cancer
ErbB2	Trastuzumab	Breast cancer	Approved	Phase III
	Lapatinib	Breast cancer	Approved	Phase III
c-Met	ARQ197	Lung cancer	Phase III	Phase II
	Foretinib	Solid tumor	Phase II	Phase II
FGFR2	Brivanib	Hepatocellular carcinoma	Phase III	
	TSU68	Hepatocellular carcinoma	Phase I/II	
EGFR	Gefitinib	Lung cancer	Approved	Phase II
	Erlotinib	Lung cancer	Approved	Phase II
	Cetuximab	Colorectal cancer	Approved	Phase III
	Panitumumab	Colorectal cancer	Approved	Phase III
VEGFR	Bevacizumab	Colorectal cancer	Approved	Phase III
	Sunitinib	Renal cell carcinoma	Approved	Phase II
VEGFR/RAF	Sorafenib	Hepatocellular carcinoma	Approved	Phase II
mTOR	Everolimus	Renal cell carcinoma	Approved	Phase III
	Temsirolimus	Renal cell carcinoma	Approved	
BRAF	PLX-4032	Melanoma	Phase I	
Hedgehog	GDC-0449	Medulloblastoma/basal cell carcinoma	Phase II	Phase II

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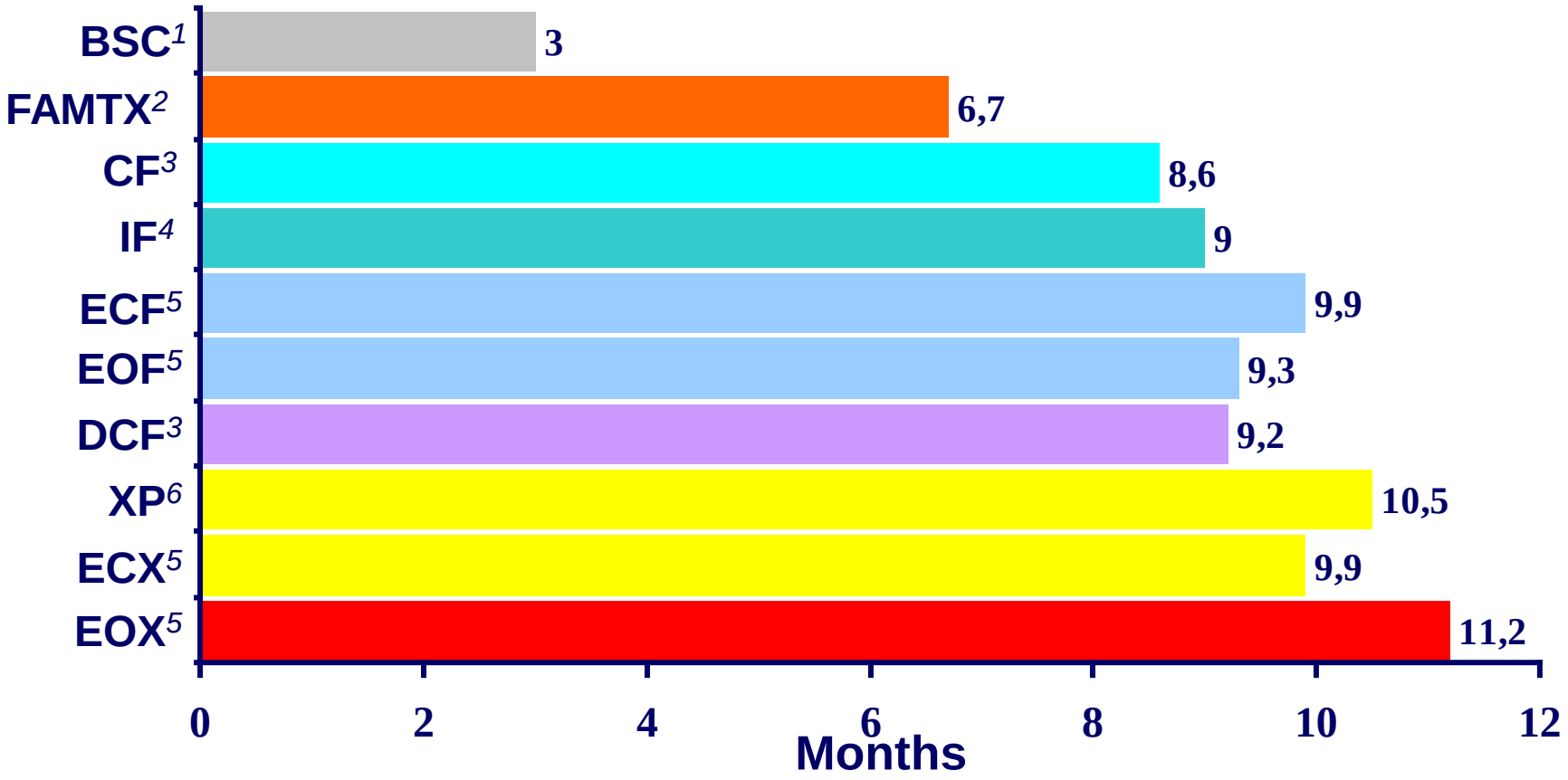
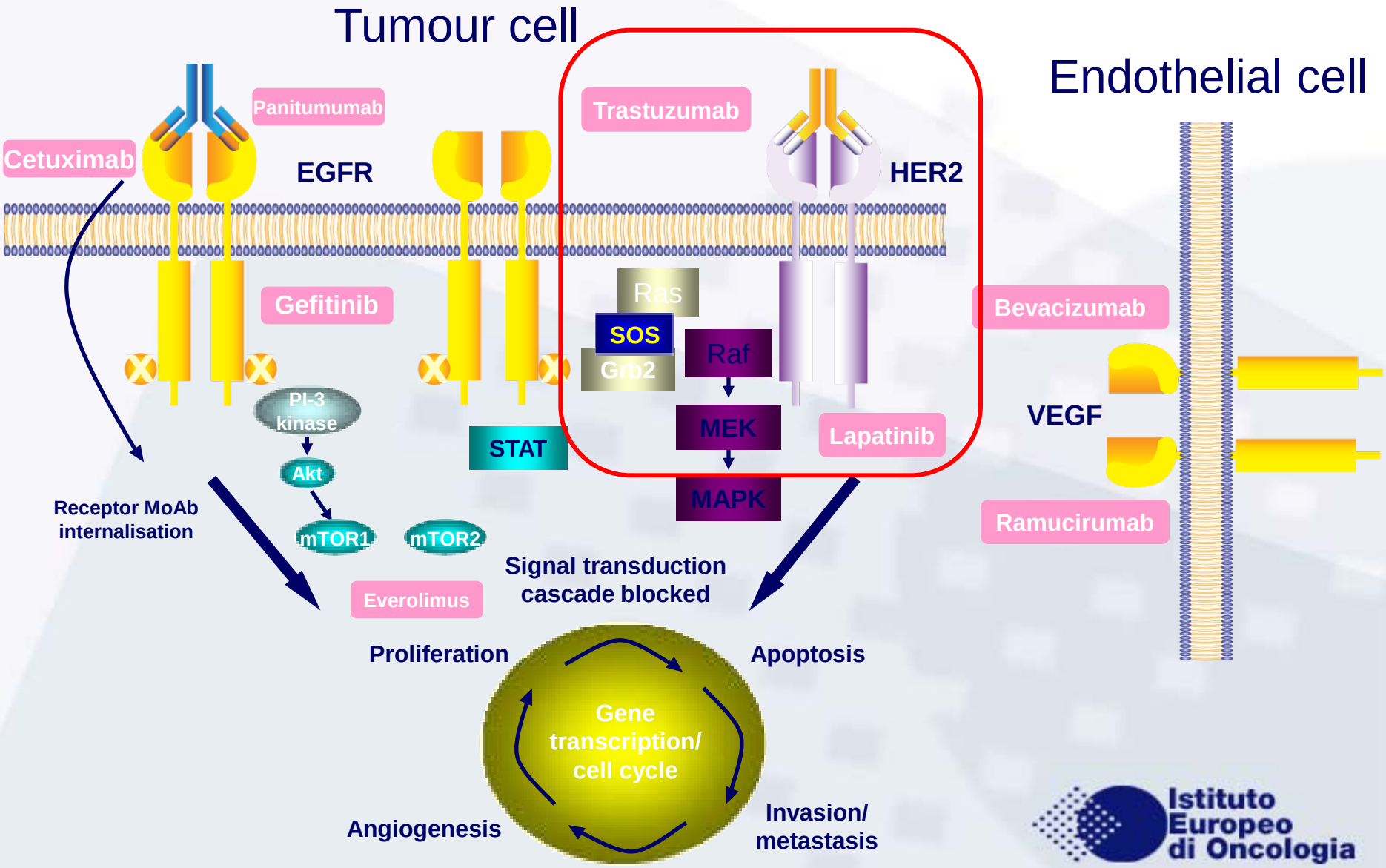
Overall survival with chemotherapy in advanced OG cancer



[1]Murad et al. Cancer 1993; [2]Vanhoefer et al. J Clin Oncol 2000; [3]Van Cutsem et al. J Clin Oncol 2006; [4]Dank et al. Ann Oncol 2008; [5]Cunningham et al. N Engl J Med 2008;
[6]Kang et al. Ann Oncol 2009

Multiple targets and agents in Gastric cancer



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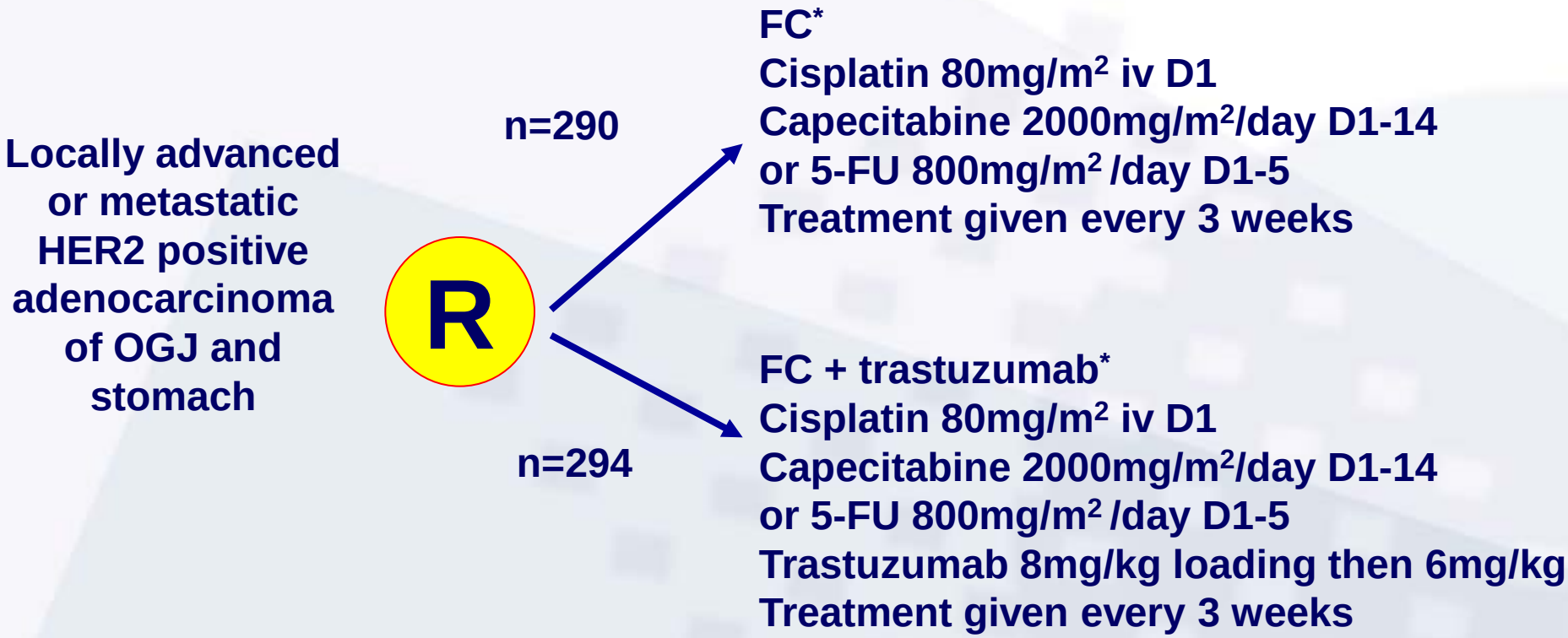
Phase III trastuzumab global registration in AGC trial design

(ToGA)



Primary objective: superiority in OS with FC +T

*88% of patients received capecitabine

Bang et al. The Lancet 2010

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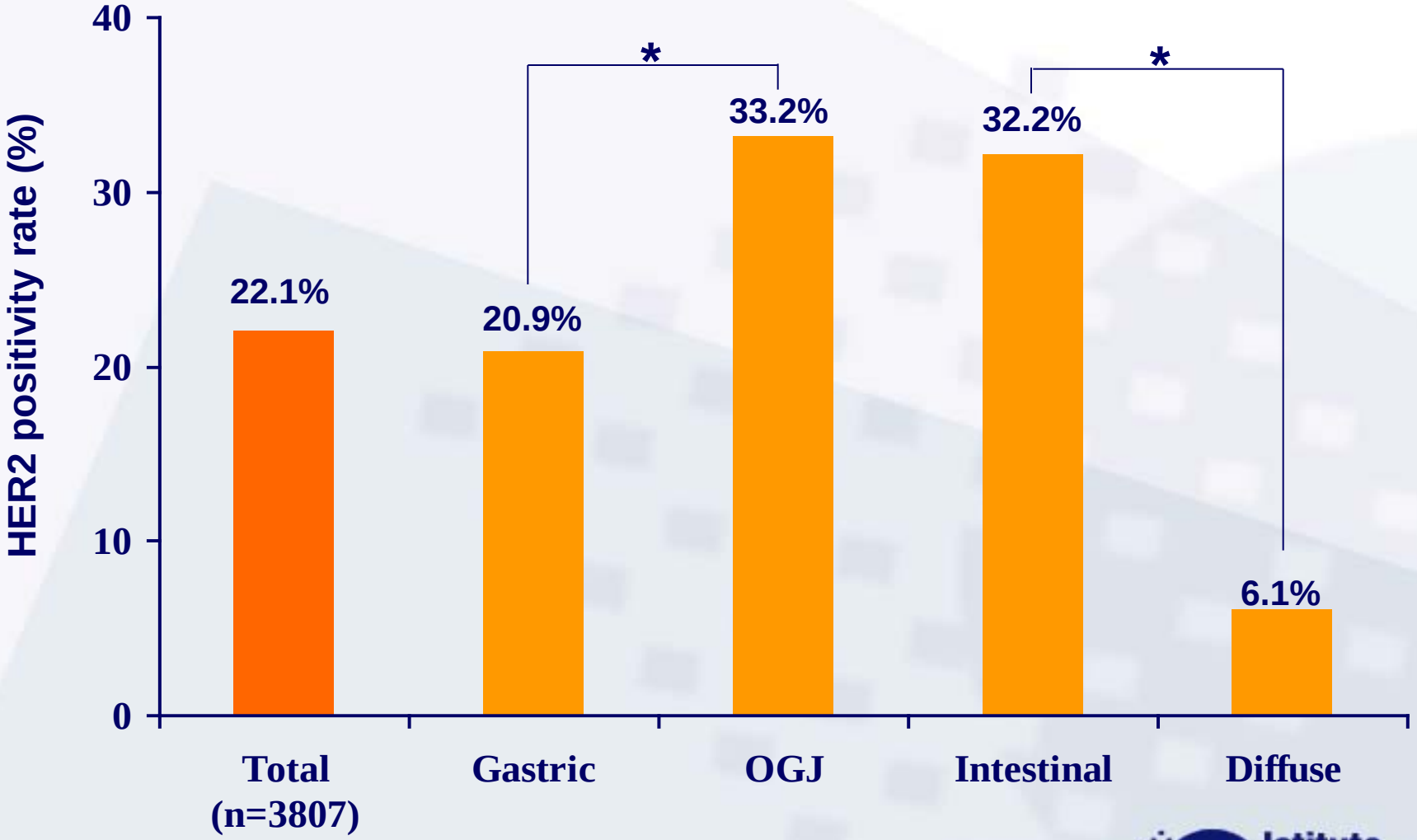
ToGA global screening programme: HER2 positivity rates in GC



*p<0.001

Bang et al ASCO 2009

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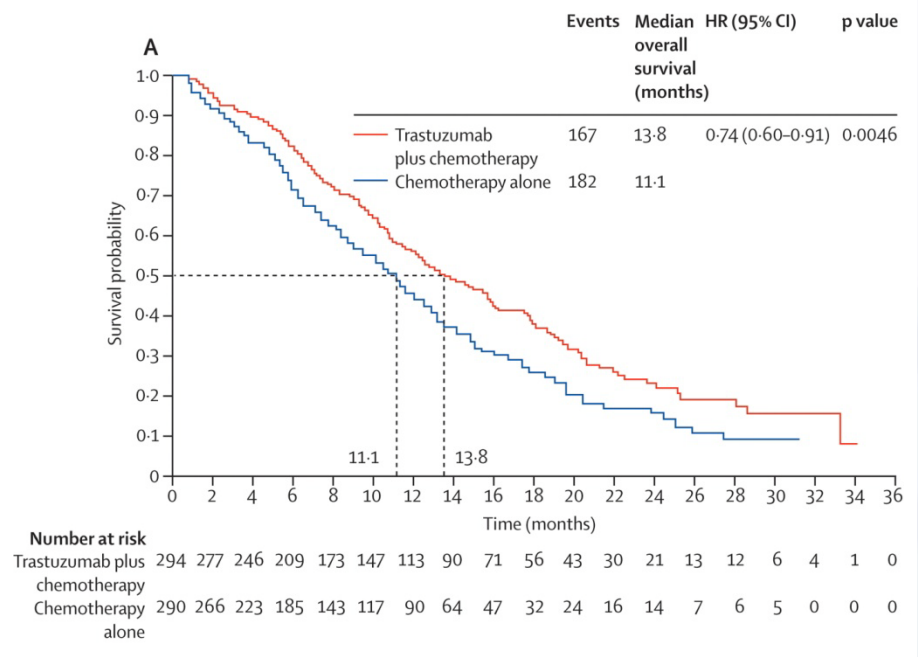
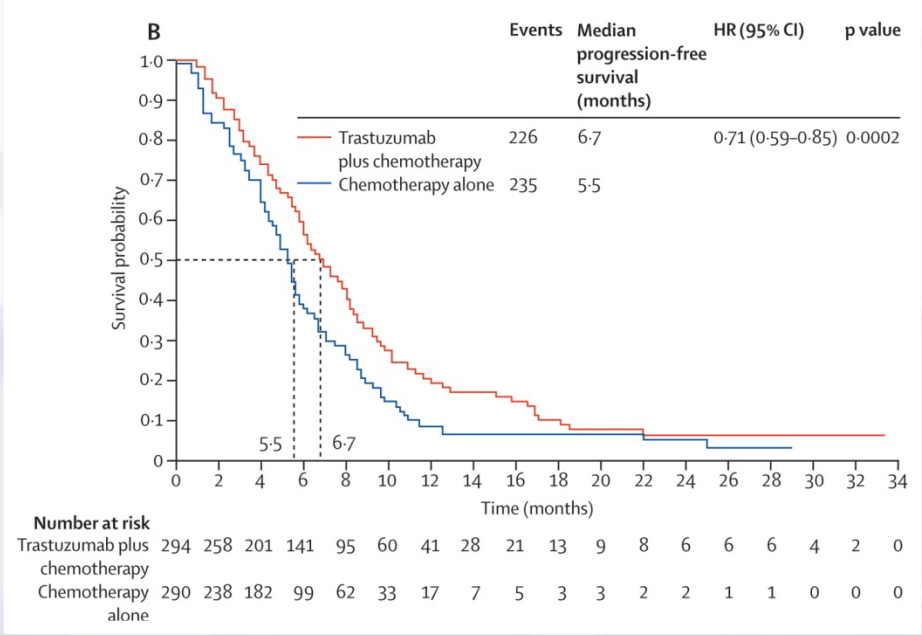
TOGA survival

Overall survival



Progression free survival



Bang et al The Lancet 2010

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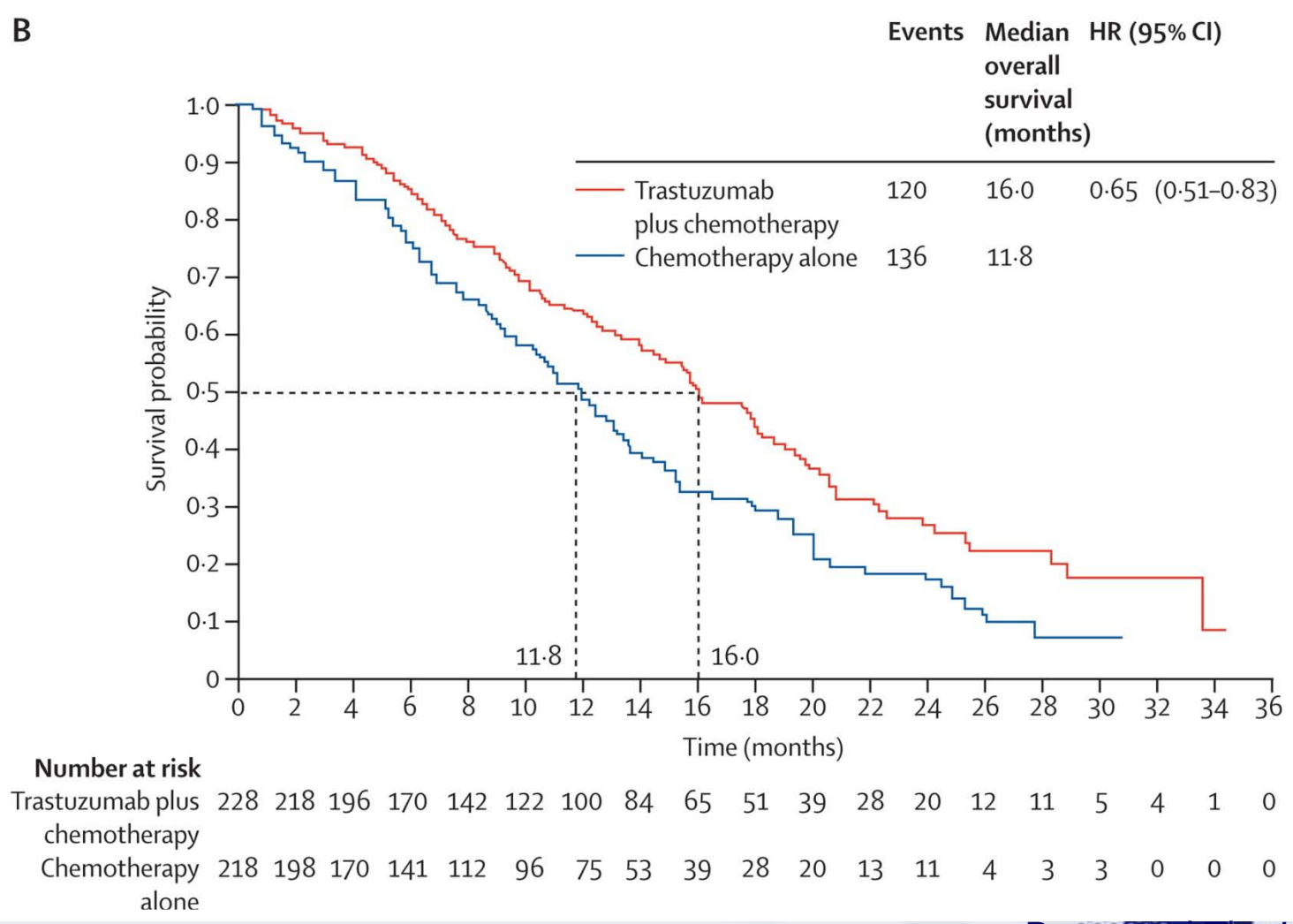
OS in FISH+ and IHC 2+/ IHC 3+ groups combined



Bang et al. The Lancet 2010

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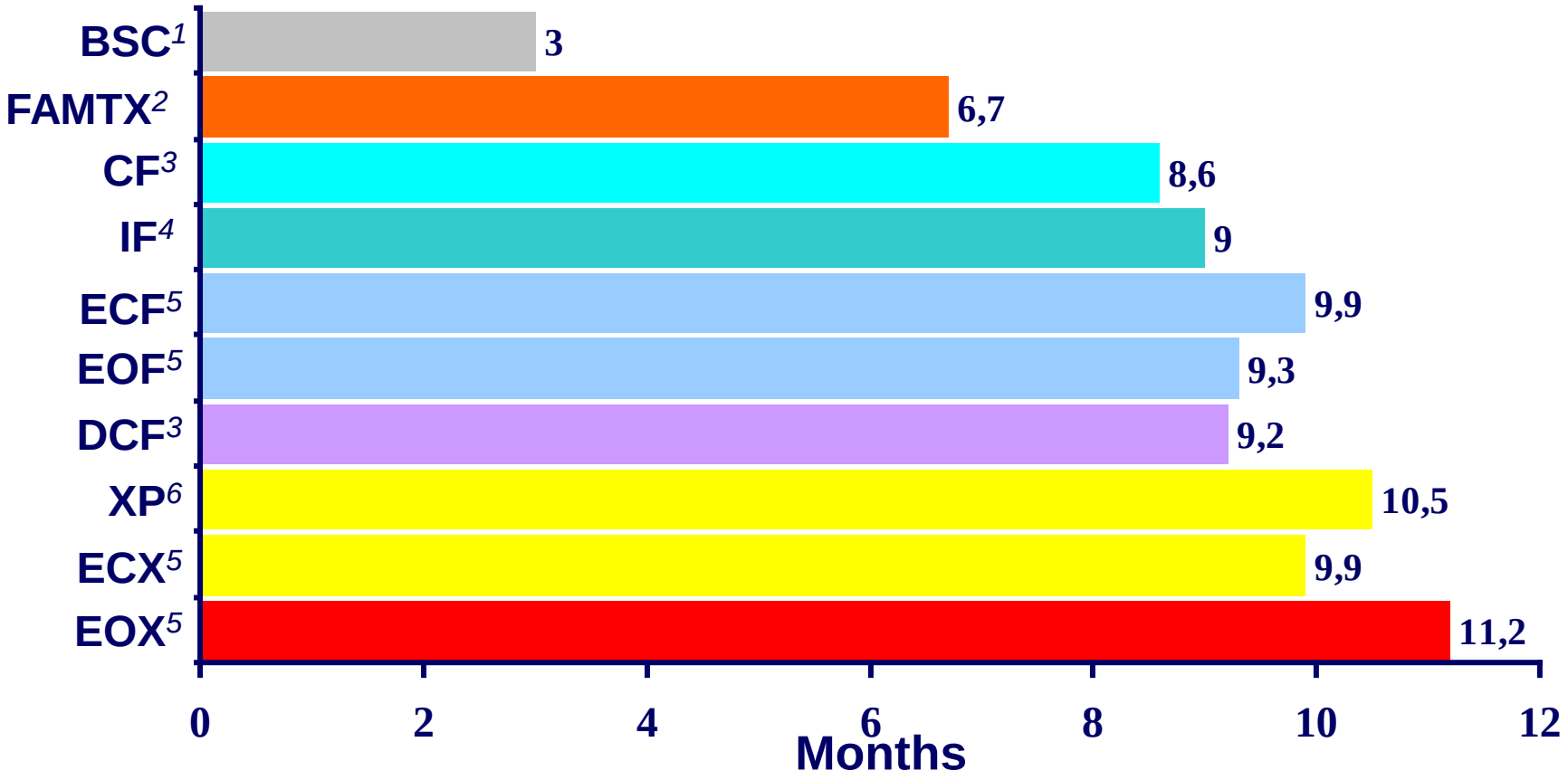
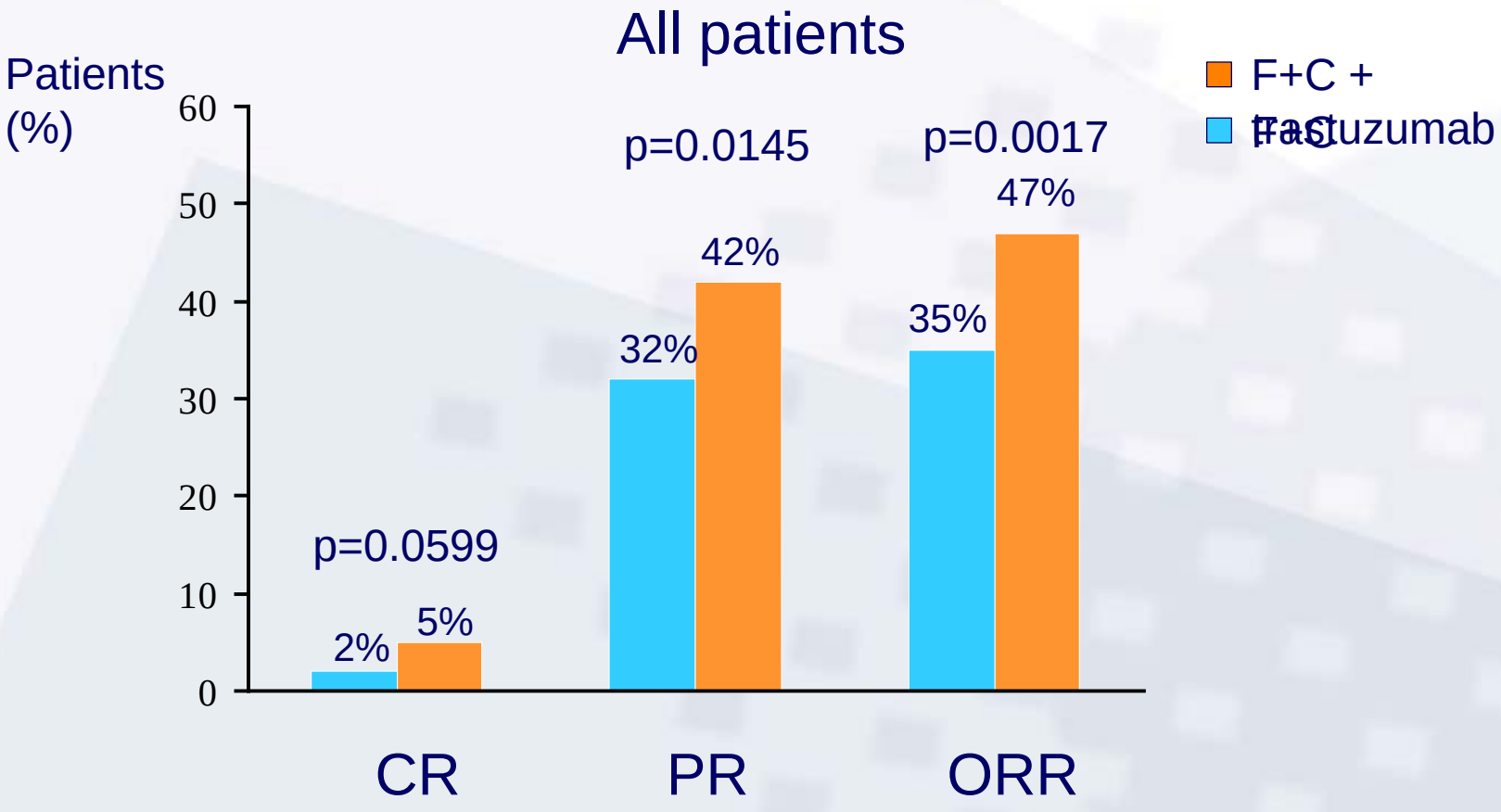
Overall survival with chemotherapy in advanced OG cancer



[1]Murad et al. Cancer 1993; [2]Vanhoefer et al. J Clin Oncol 2000; [3]Van Cutsem et al. J Clin Oncol 2006; [4]Dank et al. Ann Oncol 2008; [5]Cunningham et al. N Engl J Med 2008;
[6]Kang et al. Ann Oncol 2009

Tumour response rate



ORR= CR + PR
CR, complete response; PR, partial response

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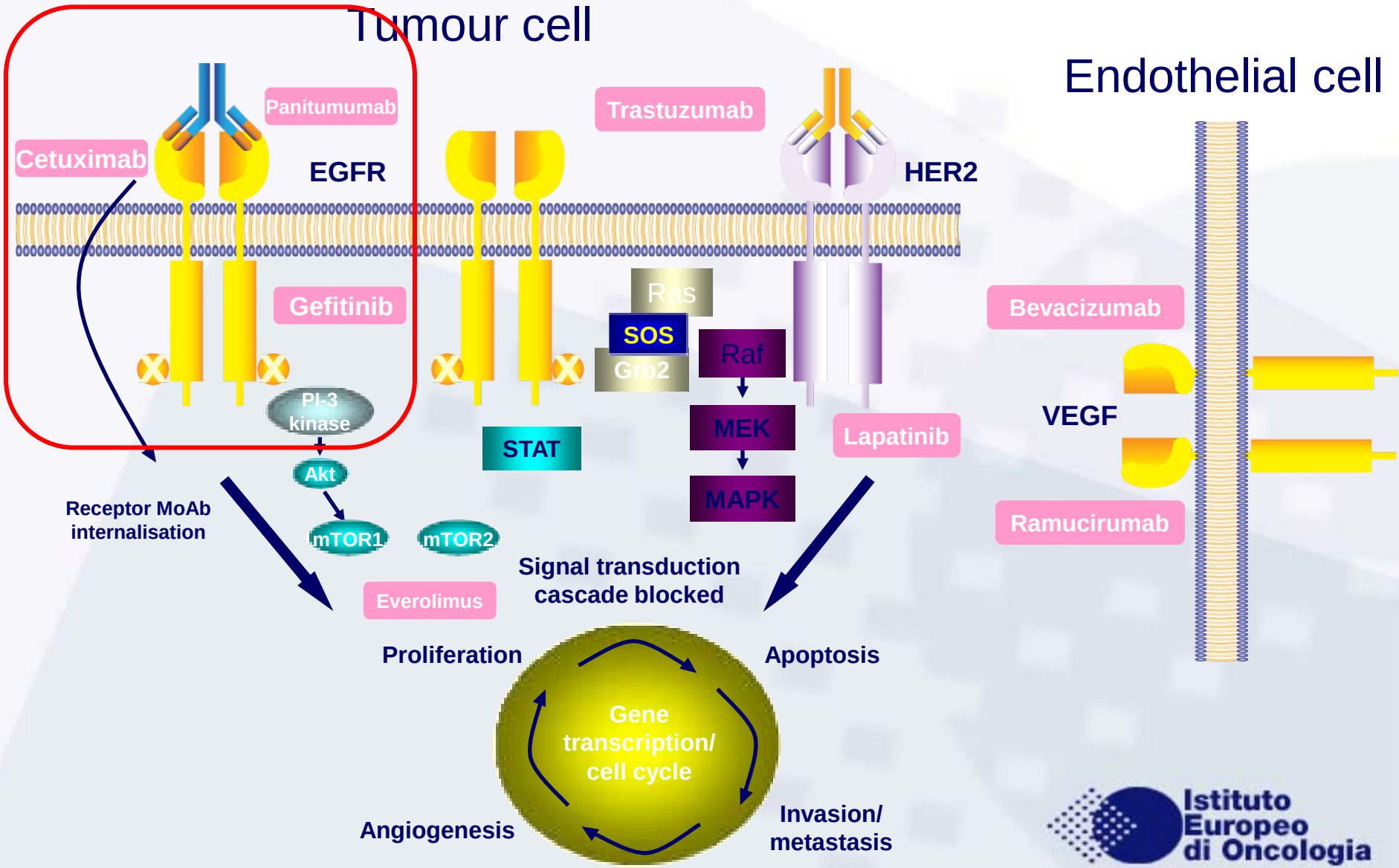
Multiple targets and agents in Gastric cancer



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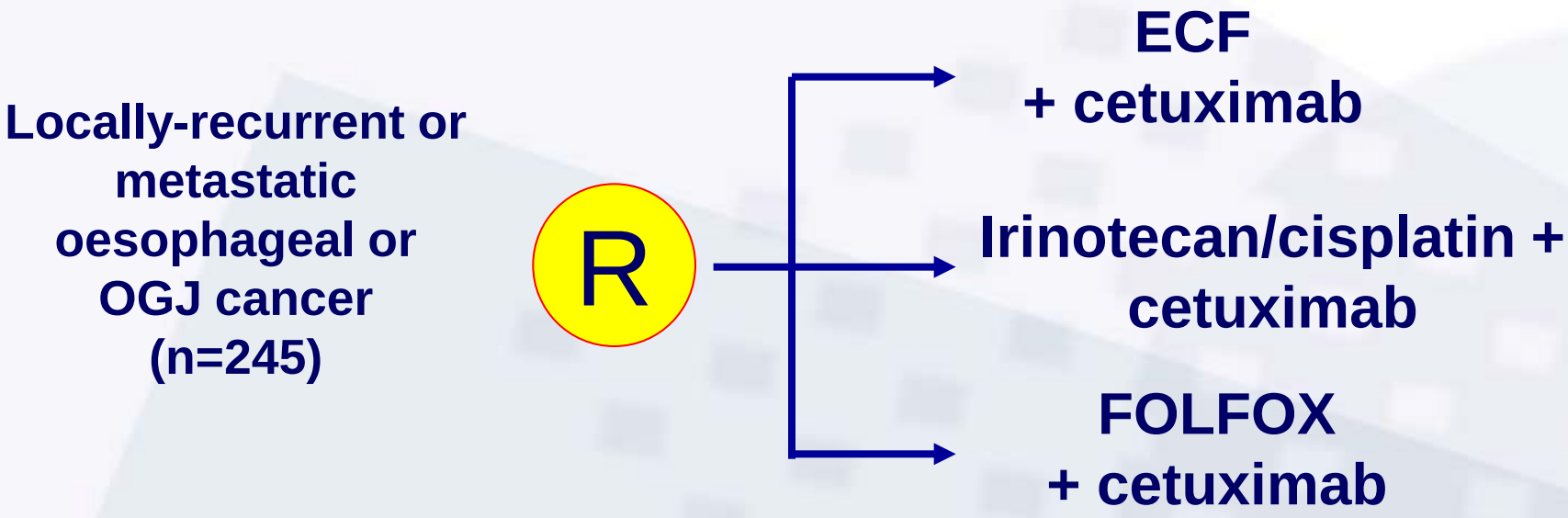
CALGB 80403/ECOG 1206 Phase II trial



- Primary endpoint: ORR
- Enrollment: September 2006 to May 2009

Enzinger et al. ASCO 2010

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CALGB 80403/ECOG 1206: ASCO results

	ECF-C (n=67)	IC-C (n=71)	FOLFOX-C (n=72)
Efficacy			
ORR (%)	57.8	45.6	53.6
OS (mth)	11.5	8.9	12.4
PFS (mth)	5.9	5.0	6.7
TTF (mth)	5.5	4.5	6.7
Toxicity (gr 3–5) (%)			
Haematological	49	58	46
Neutropenia	48	49	42
Gastrointestinal	28	42	22
Neurological	12	4	17
Infection	13	8	7
Treatment modification (%)	90	86	72

Enzinger et al. ASCO 2010

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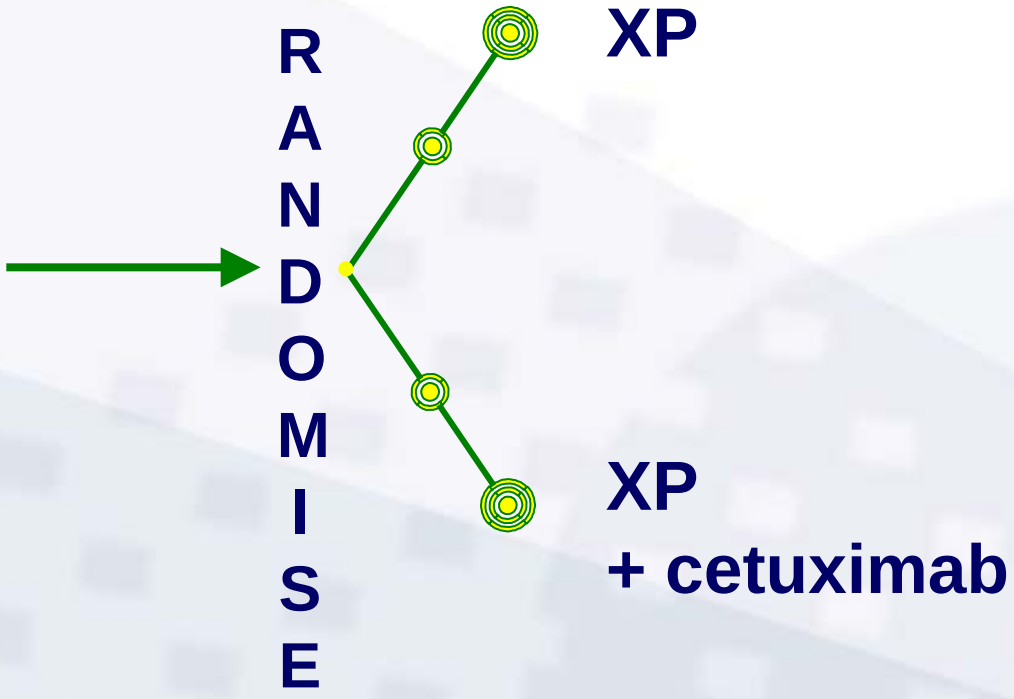
EXPAND trial design

Locally advanced or metastatic adenocarcinoma of OGJ and stomach



- Primary endpoint: overall survival
- Target recruitment: 870 patients
- Enrolment began: June 2008 – Dec 2010

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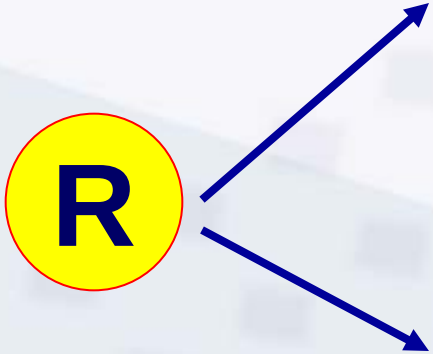
REAL-3: Phase III trial of EOX ± panitumumab

Locally advanced or metastatic adenocarcinoma or undifferentiated carcinoma of oesophagus, OGJ and stomach



EOX
Epirubicin 50mg/m^2
Oxaliplatin 130mg/m^2
Capecitabine 1250mg/m^2

EOX + panitumumab
Epirubicin 50mg/m^2
Oxaliplatin 100mg/m^2
Capecitabine 1000mg/m^2
Panitumumab 9mg/kg

- Primary endpoint: overall survival
- Target recruitment: 730 patients
- No pre-selection for K-ras wild-type patients

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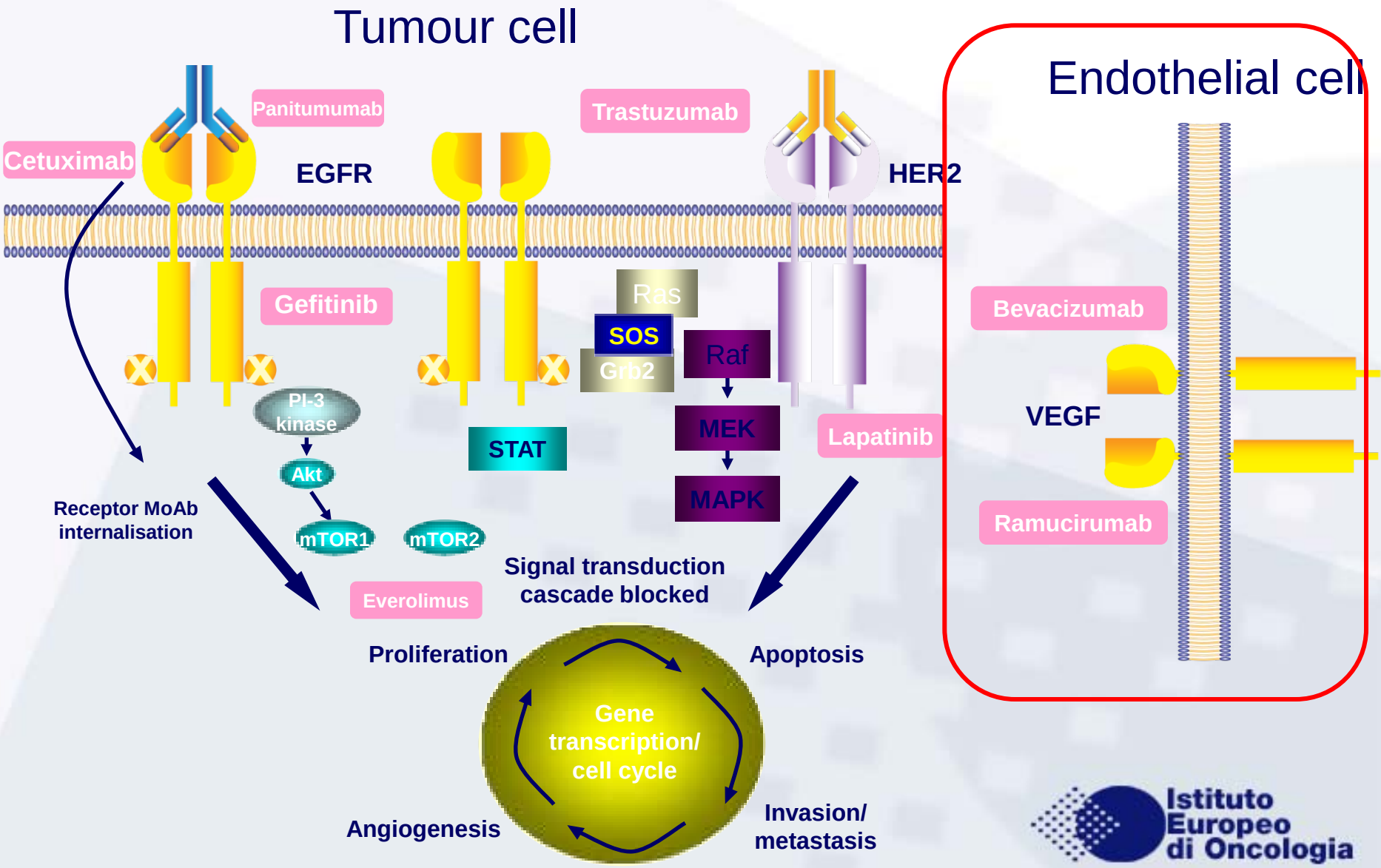
Multiple targets and agents in Gastric cancer



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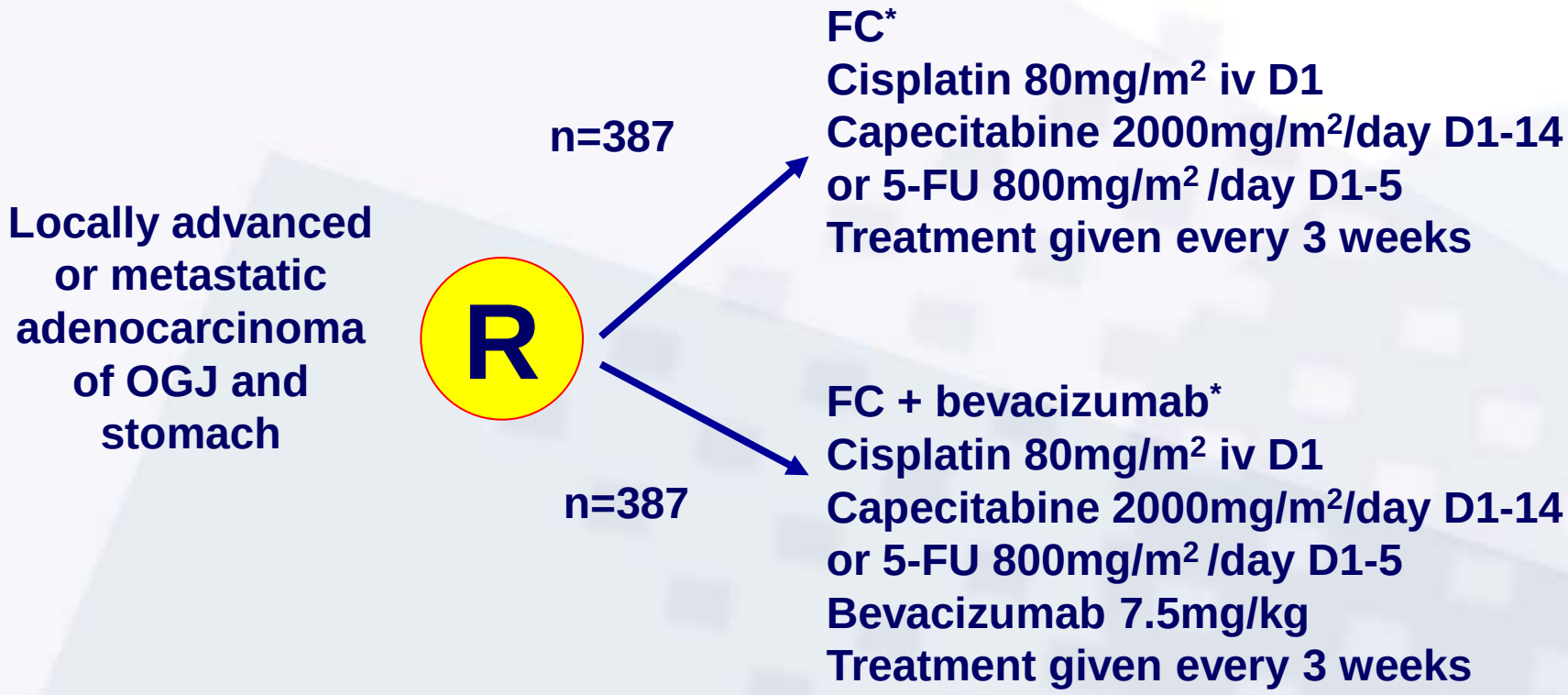
Phase III bevaciuzmab global registration in AGC trial design

(AVASGAST)



Primary objective: superiority in OS with FC +B

*94% of patients received capecitabine

Kang et al ASCO 2010

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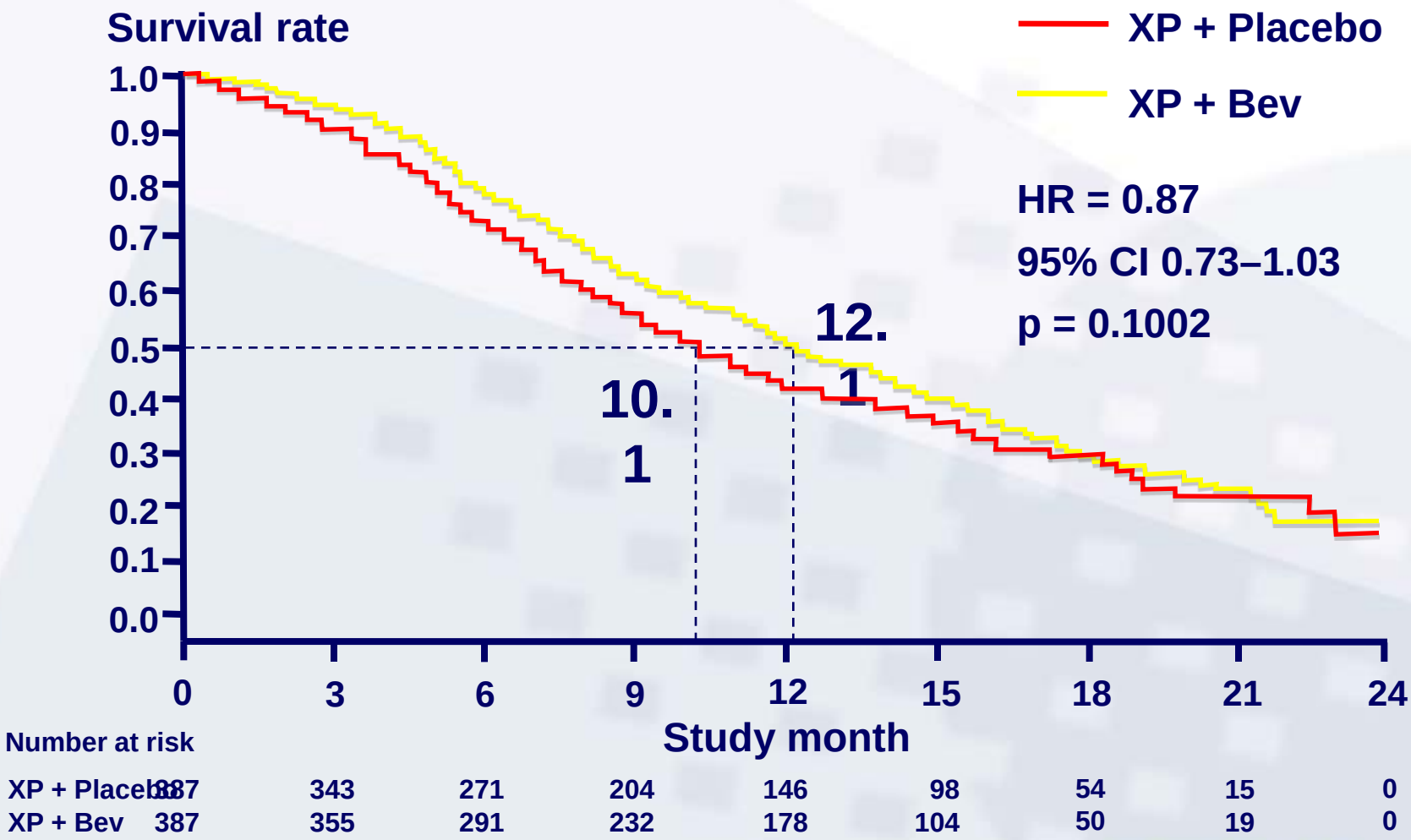
AVASGAST: Overall Survival



Kang et al ASCO 2010

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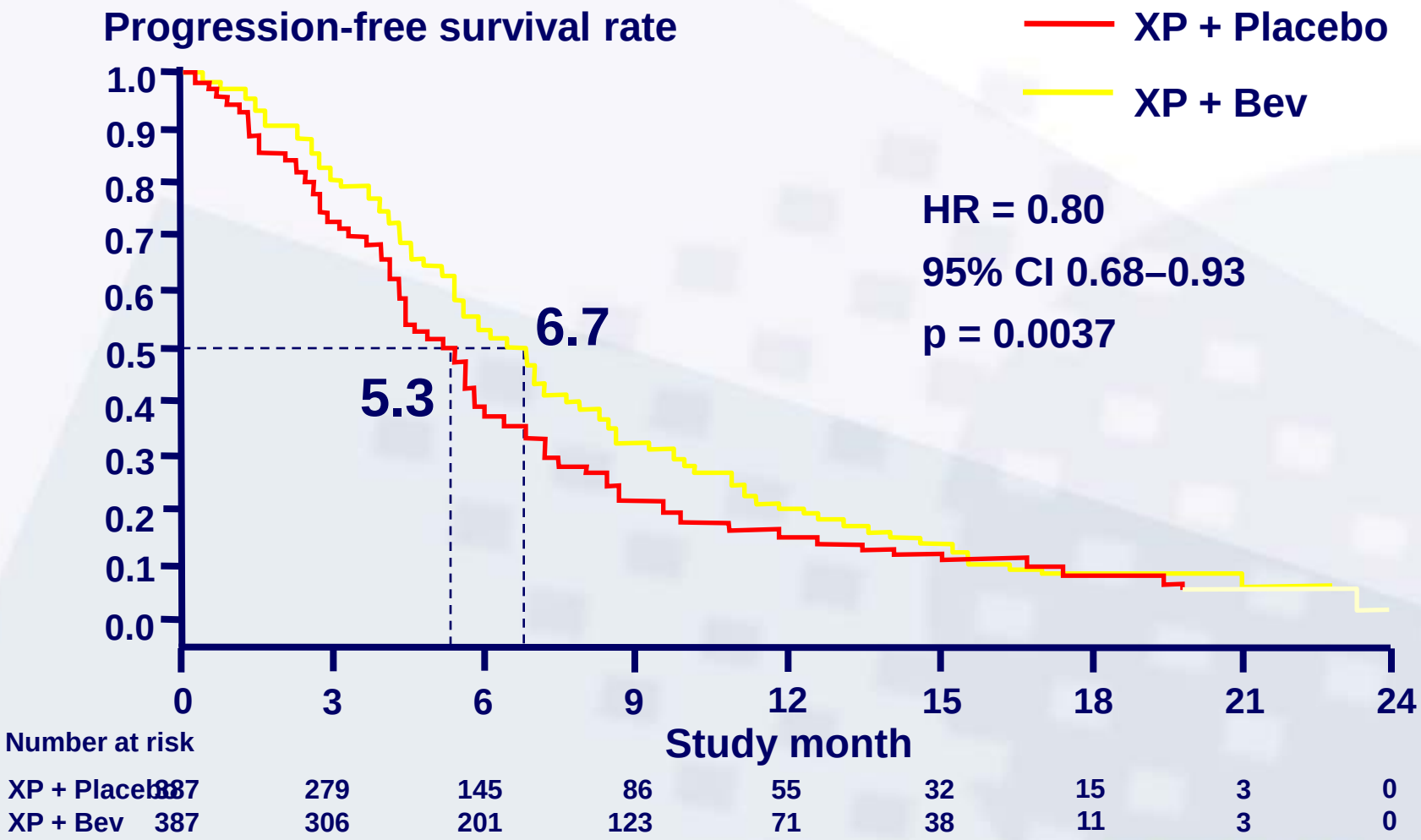
AVAGAST: Progression-Free Survival



Kang et al ASCO 2010

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Best Overall Response:
Measurable Disease Population

	XP + Placebo N=387	XP + Bev N=387
Patients with measurable disease	297	311
Overall response	111 (37%)	143 (46%)
95% CI	31.9–43.1	40.3–51.7
Difference	9%	
95% CI	0.6–16.6	
P value (χ^2)	0.0315	
Complete response	3 (1%)	5 (2%)
Partial response	108 (36%)	138 (44%)
Stable disease	90 (30%)	93 (30%)
Progressive disease	63 (21%)	44 (14%)
Not assessable	33 (11%)	31 (10%)

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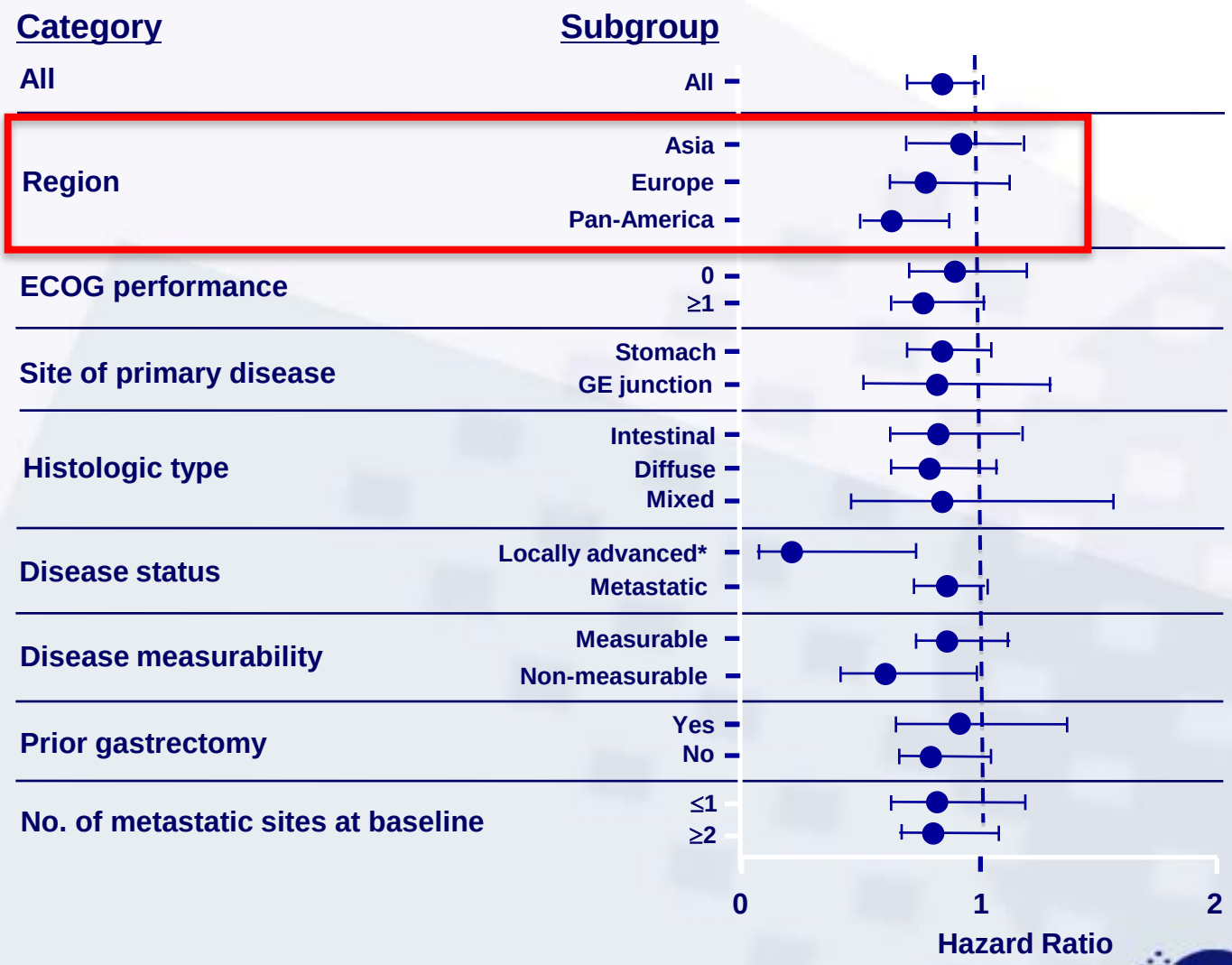
Overall Survival: Subgroup Analysis



* 29 patients with locally advanced disease only

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Regional differences in efficacy

	Region	XP + Placebo Median, mo	XP + Bev Median, mo	Delta, mo	Hazard Ratio	95% CI
OS	Asia	12.1	13.9	1.8	0.97	0.75–1.25
	Europe	8.6	11.1	2.5	0.85	0.63–1.14
	America	6.8	11.5	4.7	0.63	0.43–0.94
PFS	Asia	5.6	6.7	1.1	0.92	0.74–1.14
	Europe	4.4	6.9	2.5	0.71	0.54–0.93
	America	4.4	5.9	1.5	0.65	0.46–0.93

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Second-line therapy by region

Region	Patients entered	Patients receiving second-line treatment	%
Asia	376	248	66
Europe	249	78	31
Pan-America	149	32	21

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JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Genetics of Biliary Tract Cancers and Emerging Targeted Therapies

Aram F. Hezel, Vikram Deshpande, and Andrew X. Zhu

From the James P. Wilmot Cancer Center, University of Rochester School of Medicine, Rochester NY; and Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA.

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ABSTRACT

Biliary tract cancers (BTC), which encompass intra- and extrahepatic cholangiocarcinomas and gallbladder carcinomas, are a genetically diverse collection of cancers. Evidence suggests distinct models of molecular and pathologic progression, and a growing body of genetics data points to a heterogeneous collection of underlying mutations in key oncogenes and tumor suppressor genes. Although tumor genetics have been used to tailor individual treatment regimens and guide clinical decision making in other cancers, these principles have not been applied in BTC. Recent clinical trials with targeted therapies seem promising, although the relationships between subsets of patients with positive responses to therapy and tumor genetics remain unexplored. Here, we summarize the molecular pathogenesis and genetics of BTCs and animal modeling and relate these to recent and ongoing clinical trials with targeted agents.

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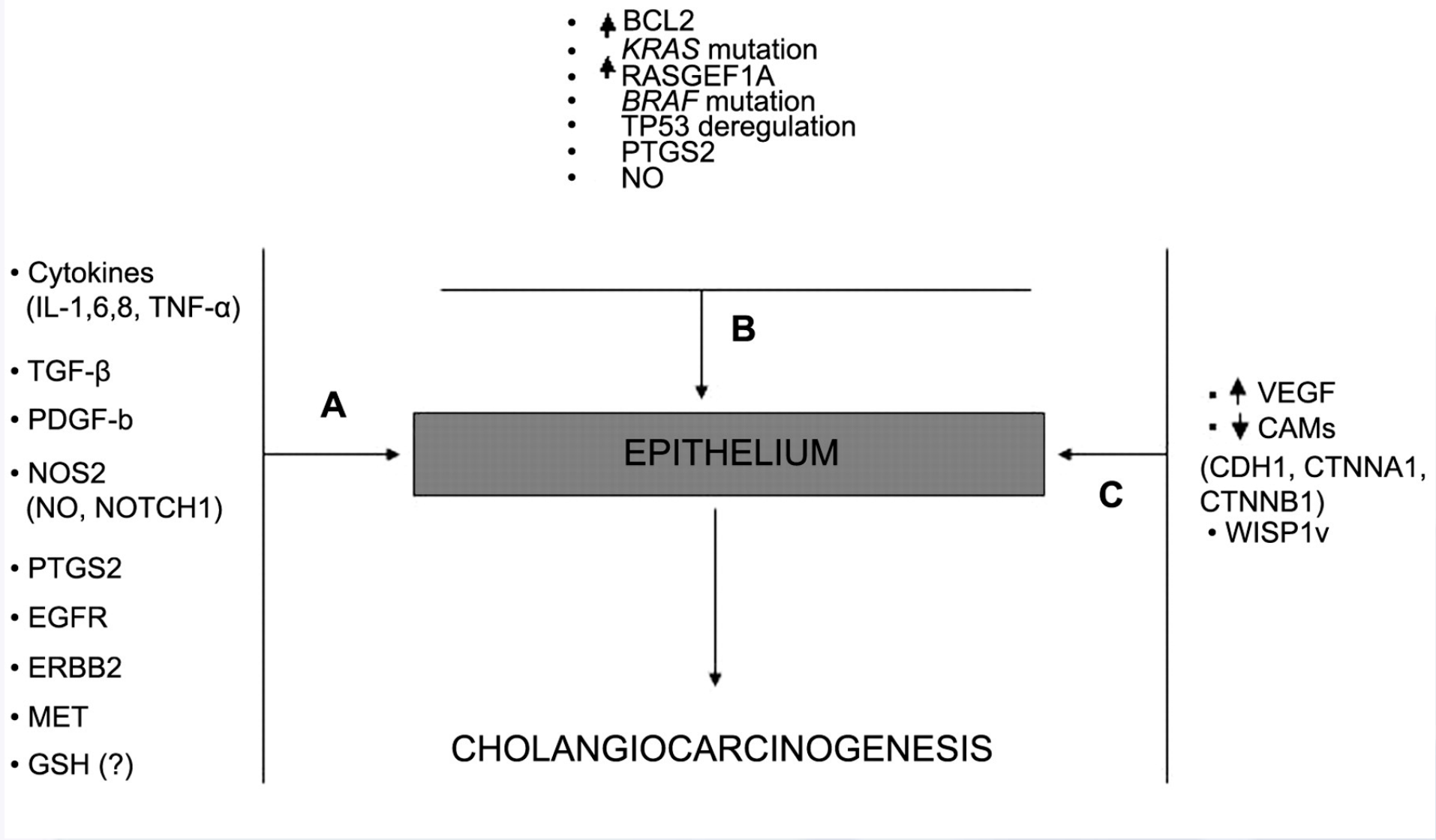

A: Tumor Initiation; B: Tumor Promotion; C: Tumor Progression

Hassid et al, Anticancer Res 2009

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Mutational Spectrum of Oncognes in Biliary Tracts Cancer

Gene and Reference	Gallbladder Carcinoma (%)	Cholangiocarcinoma (%)		Detection Method
		EHCC	IHCC	
CTNNB1/β-catenin				
Yanagisawa et al[28]	5			SEQ
Rashid et al[29]	9	0		SEQ
Chang et al[30]	0			SEQ
KRAS				
Hanada et al[27]	38			PCR-SSCP
Kim et al[31]	20			PCR-RFLP
Watanabe et al[32]	19			PCR-RFLP
Rashid et al[36]	3	15		SEQ
Suto et al[37]		10		PCR-SSCP
Tannapfel et al[38]			54	SEQ
Tannapfel et al[35]			45	SEQ
Ohashi et al[39]			48	SEQ
BRAF				
Saetta et al[40]	33			SEQ
Tannapfel et al[35]			22	SEQ
Goldenberg et al[41]	0	0	0	SEQ and GLCR
EGFR				
Leone et al[42]	9	18	20	SEQ
Gwak et al[43]		6		SEQ
Nakazawa et al[44]	12	5	10	IHC and FISH
PIK3CA				
Riener et al[45]	4	0	9	SEQ
ERBB2/HER2				
Nakazawa et al[44]	16	5	0	IHC and FISH

Abbreviations: EHCC, extrahepatic cholangiocarcinoma; IHCC, intrahepatic cholangiocarcinoma; SEQ, sequencing; PCR, polymerase chain reaction; SSCP, single-strand confirmation polymorphism; RFLP, restriction fragment length polymorphism; GLCR, gap ligase chain reaction; IHC, immunohistochemistry; FISH, fluorescent in situ hybridization.

Hezel et al, JCO 2010

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Mutational Spectrum of Tumor Suppressor Genes in Biliary Tracts Cancer

Gene and Reference	Gallbladder Carcinoma (%)	Cholangiocarcinoma (%)		Detection Method
		EHCC	IHCC	
P16INK4A				
Kim et al[31]	31			SSCP
Ueki et al[53]	62	55		Numerous
Tannapfel et al[38]			88	Numerous
TP53				
Kim et al[31]	36			SSCP
Suto et al[37]		33		PCR-SSCP
Tannapfel et al[54]			37	SEQ
SMAD4				
Hahn et al[55]		16		PCR-SSCP
Argani et al[56]		55	13	IHC
STK11/LKB1				
Su et al[57]		6		SEQ

Abbreviations: EHCC, extrahepatic cholangiocarcinoma; IHCC, intrahepatic cholangiocarcinoma; SSCP, single-strand confirmation polymorphism; PCR, polymerase chain reaction; SEQ, sequencing; IHC, immunohistochemistry.

Hezel et al, JCO 2010

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Mutations in Carcinogenesis

Gene and Reference	Adenoma (%)	Dysplasia (%)	Carcinoma (%)
β-Catenin			
Yanagisawa et al[28]	63		5
Rashid et al[29]	57		9
Chang et al[30]	58	0	0
KRAS			
Hanada et al[27]	17	15	38
Kim et al[31]	0	0	20
Watanabe et al[32]	0		19
Wistuba et al[33]	25		
TP53			
Kim et al[31]	0	0	36
Wistuba et al[33]	0		
P16INK4A			
Kim et al[31]	0	0	31

Hezel et al, JCO 2010

EGFR/HER2 status according to clinico-pathological features

Parameter	EGFR 2+ and 3+ tumors	P	HER2 2+ and 3+ tumors	P
Gallbladder cancer	5/13		8/34	
Mass forming type	6/24	0.088	7/47	0.517
Intraductal growth type	11/19		10/43	
Histological type				
Well differentiated	2/3		1/8	
Moderately differentiated	16/39	0.511	20/80	0.202
Poorly differentiated	4/14		4/36	
Stage[1]				
I	3/4		4/9	
II	2/6	0.317	4/20	0.059
III	8/17		9/31	
IV	9/29		8/64	
Chemotherapy				
Partial response	2/3		4/9	
Stable disease	3/13	0.296	4/27	0.156
Progressive disease	5/13		5/26	

Harder, World G Gastroenterol 2009

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Molecularly Targeted Trials

Treatment	Target	No. of Patients	RR (%)	PFS	Reference
Multiple agents (first line)					
GEMOX		50	NA	44% (4 months)	
GEMOX-cetuximab	*EGFR*	51	NA	61% (4 months)	Malka et al[98]
GEMOX-bevacizumab	*VEGF*	35	40	7 months (median)	Zhu et al[104]
Single agents (first and second line)					
AZD6244	*MEK1/2*	22	14	5.4 months (median)	Bekaii-Saab et al[101]
Erlotinib	*EGFR*	43	7	2.6 months (median)	Philip et al[99]
Lapatinib	*EGFR/HER2*	17	0	1.8 months (median)	Ramanathan et al[100]
Sorafenib	*BRAF/VEGFR*	36	6	2 months (median)	El-Khoueiry et al[103]
Sorafenib	*BRAF/VEGFR*	46	2	2.3 months (median)	Bengala et al[102]

Abbreviations: RR, response rate; PFS, progression-free survival; GEMOX, gemcitabine and oxaliplatin; NA, not available.

Molecularly Targeted Therapies in Development

Treatment	Target	Phase	Sponsoring Institution(s)	ClinicalTrials.gov Identification No.
Oxaliplatin, capecitabine, and sorafenib	*BRAF/VEGFR*	I/II	University of Wisconsin, Madison, WI	NCT00634751
Gemcitabine, oxaliplatin, and sorafenib	*BRAF/VEGFR*	I/II	University of Miami Sylvester Comprehensive Cancer Center, Miami, FL	NCT00955721
Erlotinib and docetaxel	*EGFR*	II	Hoosier Oncology Group, Indianapolis , IN	NCT00532441
BIBW 2992 in cancers with *EGFR* and/or *HER2* gene amplification	*EGFR/HER2*	II	Massachusetts General Hospital Cancer Center, Boston, MA	NCT00748709
FOLFOX6 and bevacizumab	*VEGF*	II	Georgetown University, Washington, DC	NCT00881504
Gemcitabine, cisplatin, and sorafenib	*BRAF/VEGFR*	II	Memorial Sloan-Kettering Cancer Center, New York, NY	NCT00919061
Gemcitabine, capecitabine, and vandetanib	*VEGFR/EGFR*	I/II	University of Colorado at Denver and Health Sciences Center, Denver, CO	NCT00551096
ARRY-438162	*MEK*	I/II	Sarah Cannon Research Institute, Nashville, TN	NCT00959127

Abbreviation: FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin.

Hezel et al, JCO 2010

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J Gastroenterol (2011) 46:289–296
DOI 10.1007/s00535-011-0387-9

REVIEW

Molecular targeted therapy for hepatocellular carcinoma in the current and potential next strategies

Shinji Tanaka · Shigeki Arii

Istituto Europeo di Oncologia

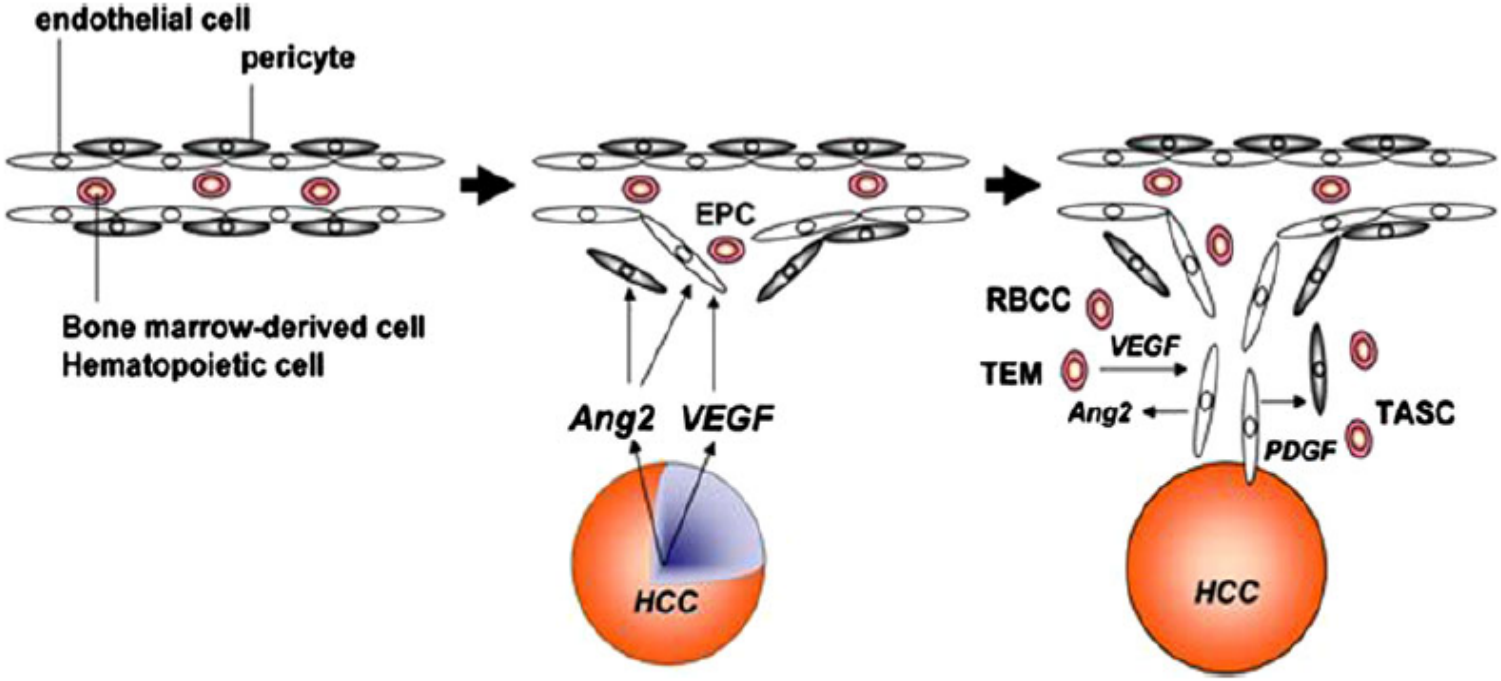

Fig. 1 Schematic demonstration of angiogenic mechanism of hepatocellular carcinoma (*HCC*). Vascular endothelial cells (*white*), pericytes (*gray*), and bone marrow-derived and/or hematopoietic cells (*red*). *EPC* endothelial progenitor cell, *RBCC* recruited bone marrow-derived circulating cell ($CXCR4^+/CD11b^+/VEGFR1^+/CD45^+$), *TEM* Tie2-expressing monocyte ($Tie2^+/CD11b^+/VEGFR1^+/CD45^+$), *TASC* tumor-associated stromal cell ($c\text{-}Kit^+/Sca1^+/VEGFR2^+/CD45^+$), *Ang2* angiopoietin-2, *VEGF* vascular endothelial growth factor, *PDGF* platelet-derived growth factor

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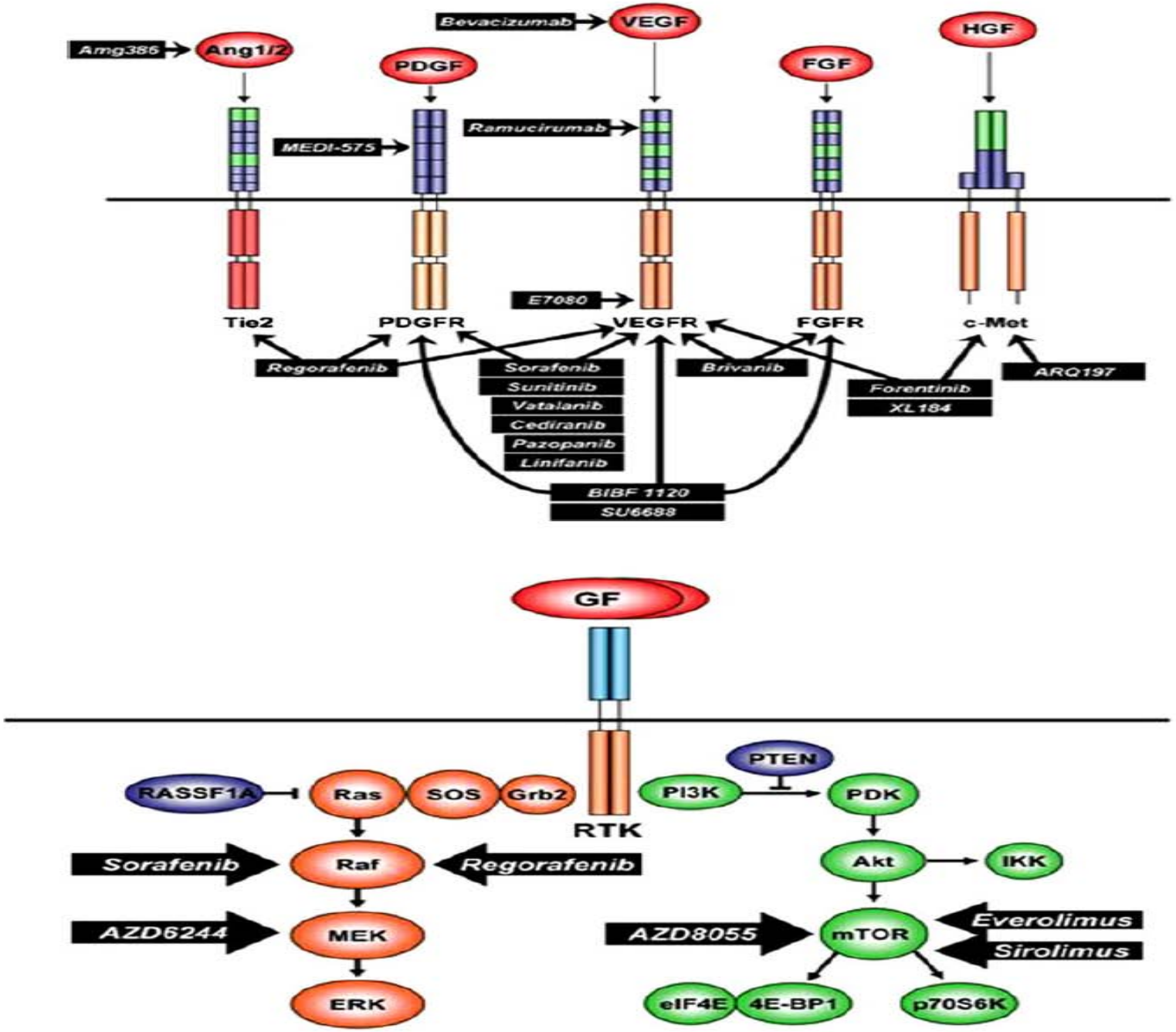
Table 1 Molecular targeted agents for hepatocellular carcinoma in relation to angiogenesis

Agent	Classification	Target
Sorafenib (Nexabar, BAY43-9006; *Bayer*)	Small-molecule compound	VEGFR2, VEGFR3, PDGFR-β, Flt-3, c-KIT tyrosine kinase, Raf serine-threonine kinase
Regorafenib (fluoro-sorafenib, BAY73-4506; *Bayer*)	Small-molecule compound	VEGFR2, VEGFR3, PDGFR-β, Flt-3, c-KIT, Tie2 tyrosine kinase, Raf serine-threonine kinase
Sunitinib (Sutent, SU11248; *Pfizer*)	Small-molecule compound	VEGFR1 VEGFR2, PDGFRs, Flt-3, c-KIT tyrosine kinase
Brivanib (BMS-582664; *Bristol-Myers Squibb*)	Small-molecule compound	VEGFR2, VEGFR3, FGFR tyrosine kinase
BIBF 1120 (Vargatef; *Boehringer Ingelheim*)	Small-molecule compound	VEGFR2, PDGFR-β, FGFR tyrosine kinase
SU6688 (TSU-68; *Taiho*)	Small-molecule compound	VEGFR2, PDGFR-β, FGFR tyrosine kinase
Vatalanib (PTK787/ZK222584; *Novartis-Schering*)	Small-molecule compound	VEGFR1, VEGFR2, VEGFR3, PDGFR-β, c-KIT tyrosine kinase
Cediranib (AZD2171; *AstraZeneca*)	Small-molecule compound	VEGFR1, VEGFR2, VEGFR3, PDGFRs, c-KIT tyrosine kinase
Pazopanib (Votrient, GW786034; *GlaxoSmithKline*)	Small-molecule compound	VEGFR-1, VEGFR-2, VEGFR-3, PDGFRs, c-KIT tyrosine kinase
Linifanib (ABT-869; *Abbott*)	Small-molecule compound	VEGFR-2, PDGFR-β, CSF-1R tyrosine kinase
E7080 (*Eisai*)	Small-molecule compound	VEGFR3, VEGFR2, VEGFR1 tyrosine kinase
Foretinib (XL880, GSK1363089; *GlaxoSmithKline*)	Small-molecule compound	VEGFR-2, c-MET tyrosine kinase
XL184 (BMS907351; *Bristol-Myers Squibb*)	Small-molecule compound	VEGFR-2, c-MET tyrosine kinase
ARQ 197 (*Daiichi Sankyo*)	Small-molecule compound	c-MET tyrosine kinase
Bevacizumab (Avastin; *Roche/Genentech*)	Monoclonal antibody	VEGF-A (neutralization)
Ramucirumab (IMC-1121B; *Eli Lilly*)	Monoclonal antibody	VEGFR-2 (neutralization)
MEDI-575 (*AstraZeneca*)	Monoclonal antibody	PDGFR-α (neutralization)
AMG 386 (*Amgen*)	Antibody-type peptide	Angiopoietin-1, angiopoietin-2 (neutralization)
Thalidomide (Thado; *TTY Biopharm*)	Small-molecule compound	FGF8, etc.
Oxi4503 (*OXiGENE*)	Small-molecule compound	vascular disrupting agent (VDA)


Bevacizumab
VEGF
HGF
Amg386
Ang1/2
PDGF
FGF
MEDI-575
Ramucirumab
E7080
Tie2
PDGFR
VEGFR
FGFR
c-Met
Regorafenib
Sorafenib
Sunitinib
Vatalanib
Cediranib
Pazopanib
Linifanib
Brivanib
Forentinib
XL184
ARQ197
BIBF 1120
SU6698
GF
RTK
RASSF1A
Ras
SOS
Grb2
PTEN
PI3K
PDK
Sorafenib
Raf
Regorafenib
Akt
IKK
AZD6244
MEK
AZD8055
mTOR
Everolimus
Sirolimus
ERK
eIF4E
4E-BP1
p70S6K

Agent	Classification	Target
Erlotinib (Tarceva, OSI774; *Roche/Genentech*)	Small-molecule compound	EGFR/ErbB1/Her1 tyrosine kinase
Gefintinib (Iressa, ZD1839; *AstraZeneca*)	Small-molecule compound	EGFR/ErbB1/Her1 tyrosine kinase
Lapatinib (Tykerb, GW572016; *GlaxoSmithKline*)	Small-molecule compound	EGFR/ErbB1/Her1 and ErbB2/Her2/Neu tyrosine kinase
BMS-599626 (*Bristol-Myers Squibb*)	Small-molecule compound	EGFR/ErbB1/Her1 and ErbB2/Her2/Neu tyrosine kinase
Cetuximab (Erbitux, IMC-C225, *Bristol-Myers Squibb*)	Monoclonal antibody	EGFR/ErbB1/Her1 (neutralization)
Cixutumumab (IMC-A12; *ImClone System*)	Monoclonal antibody	IGF-IR (neutralization)
OSI-906 (*OSI Pharmaceuticals*)	Monoclonal antibody	IGF-IR/IR (neutralization)
AZD6244 (ARRY-142886; *AstraZeneca*)	Small-molecule compound	MEK serine-threonine/tyrosine kinase
Everolimus (Afinitor, RAD001; *Novartis*)	Small-molecule compound	mTOR serine-threonine kinase
Sirolimus (Rapamune; *Johnson & Johnson*)	Small-molecule compound	mTOR serine-threonine kinase
AZD8055 (*AstraZeneca*)	Small-molecule compound	mTOR serine-threonine kinase
PXD101 (Belinostat; *CuraGen/ToPo Target*)	Small-molecule compound	HDAC
LBH589 (Panobinostat; *Novartis*)	Small-molecule compound	HDAC
4SC-201 (Resminostat; *4SC AG*)	Small-molecule compound	HDAC
Vorinostat (Zolinza; *Merck*)	Small-molecule compound	HDAC
Bortezomib (Velcade PS-341; *Millennium Pharmaceuticals*)	Small-molecule compound	proteasome
PI-88 (*Progen Industries*)	Small-molecule compound	heparanase
Mapatumumab (*Human Genome Sciences*)	Monoclonal antibody	TRAIL-R1 (neutralization)
CS-1008 (*Daiichi Sankyo*)	Monoclonal antibody	TRAIL-R2 (neutralization)
AEG35156 (GEM640; *Aegera Therapeutics Inc.*)	Antisense nucleotide	XIAP
GC33 (*Chugai*)	Monoclonal antibody	Glypican-3 (neutralization)
Z-208 (*Tamibarotene; Zeria Pharmaceutical*)	Small-molecule compound	RARα (agonist)

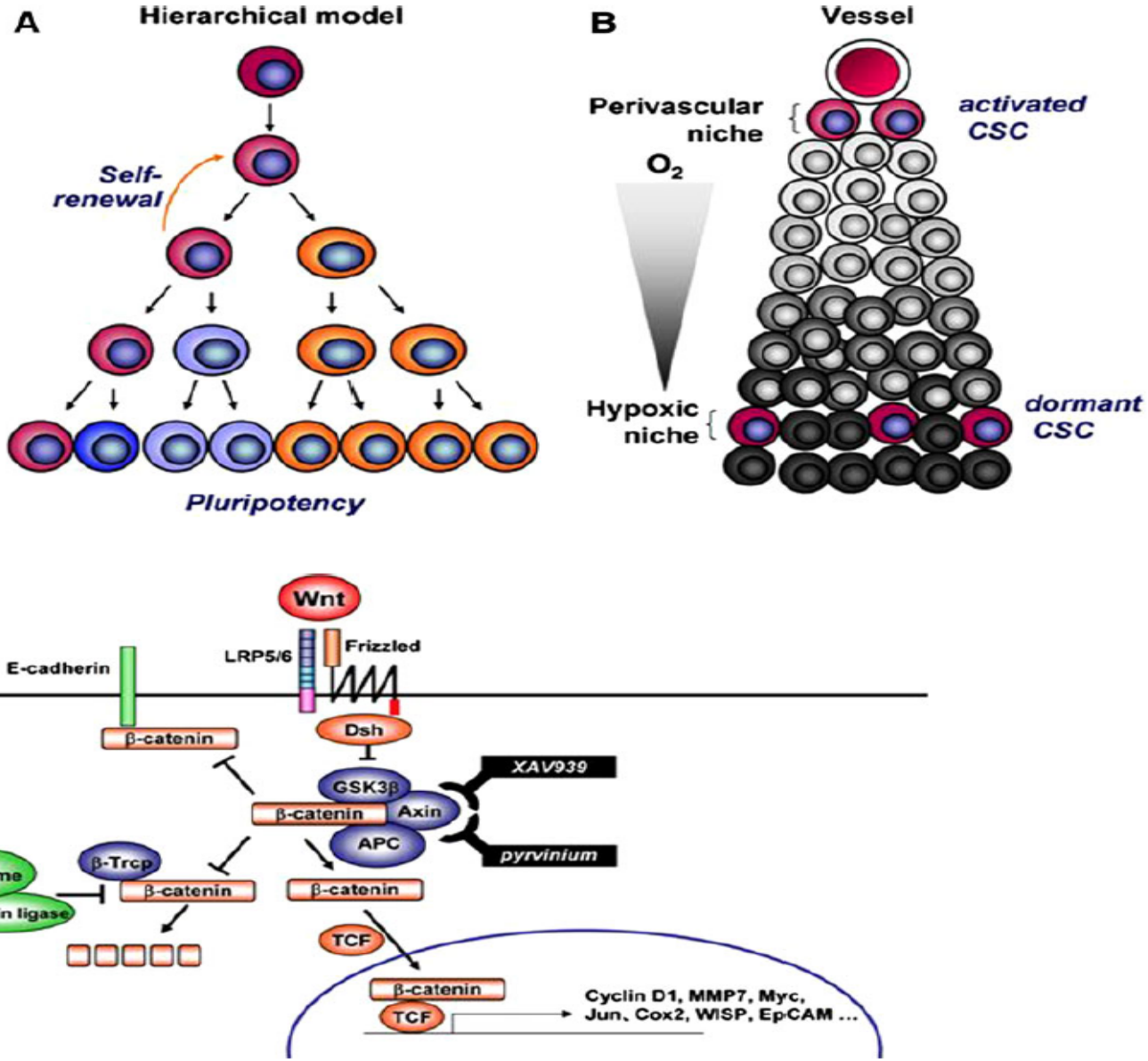


Fig. 4 Concept of cancer stem cell (*CSC*). **a** Hierarchical model of heterogeneity in cancer cells. Self-renewal and pluripotent divisions are essential in CSCs. **b** Two types of CSC niches in the tumor microenvironment. CSCs are activated in a perivascular niche around the tumor vasculature. The other niche, more distal from the vasculature, exhibits lower oxygen tension and this hypoxic niche regulates the dormant phenotype of CSCs. Activated CSCs are shown in *bright red* (*upper*) and dormant CSCs in *dark red* (*lower*)

Fig. 5 Wnt/beta-catenin signaling pathway. Wnt ligand stimulates the Frizzled receptor and inhibits GSK3 activity via the Dishevelled protein (*Dsh*). This ligand–receptor interaction requires an LPR transmembrane protein. The GSK3 phosphorylates beta-catenin in the Axin/APC complex and directs it for degradation by a beta-TRCP interaction. Unphosphorylated beta-catenin escapes recognition by beta-TRCP, which allows it to translocate to the nucleus, where it engages TCF transcription factor to regulate genes involved in cellular stemness and EMT. Novel small-molecule agents XAV939 and pyrvinium stabilize Axin protein, leading to the degradation of beta-catenin

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REVIEW

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The Molecular Targets for the Diagnosis and Treatment of Pancreatic Cancer

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Table 1. Most Common Molecular Alterations in Pancreatic Cancer and Applicable Targeted Agents

Genes	Role	Frequency of alteration	Selective targeted agents	Clinical significance
KRAS	Oncogene	74-100%	Farnesyl transferase inhibitors (FTIs) Tipirfanib, lorafarnib	• Mutation at codon 12 may be a negative prognostic factor • FTIs not active in pancreatic cancer (PC)
HER2/neu	Oncogene	16-65%	Trastuzumab, lapatinib	No therapeutic benefit
HER3	Oncogene		Lapatinib, erlotinib	Might be associated with response to erlotinib
Akt2	Oncogene	10-72%	Silencing with RNA interference (RNAi) evaluated	
Notch-1	Oncogene	50-90%	Silencing with RNAi and inhibition by curcumin, genistein evaluated	Overexpression, not mutation
COX-2	Oncogene	40-50%	Celecoxib, apricoxib	Association with poor outcome and advanced stage
p16INK4a	Oncogene	27-96%	No selective inhibitor available	Confounding data regarding its prognostic value
p53	Tumor suppressor	43-76%	No selective inhibitor available	Confounding data regarding its prognostic value Probably predictive of poor response to Rx
DPC4	Tumor suppressor	50%	No selective inhibitor available	Controversial prognostic value
BRCA2	Tumor suppressor	6-17%	No selective inhibitor available	BRCA 1/2 genes involved in DNA repair BRCA2 implicated in the familial PC Benefit from PARP1 inhibitors in breast/ovarian Ca
FHIT	Tumor suppressor	70%	No selective inhibitor available	Unknown
EGF-R	Growth factor & receptor	25-65%	Cetuximab Erlotinib (Tyrosine kinase inhibitor, TKI) Gefitinib (TKI)	Not established prognostic or predictive role yet Cetuximab not active Erlotinib (and possibly gefitinib) active when combined with gemcitabine
VEGF-R	Growth factor & receptor	Up to 90%	Bevacizumab Aflibercept (VEGF trap) Vatalanib (TKI) Vandetanib (small molecule)	No therapeutic benefit yet Studies still in progress
MMPs	Matrix proteases	?	Marimastat Tanomastat Ro 28-2653	No therapeutic benefit yet
mTOR	Protein kinase	?	Temsirolimus Everolimus	No therapeutic benefit yet

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Gastrointestinal Malignancies

Defining New Paradigms for the Treatment of Pancreatic Cancer

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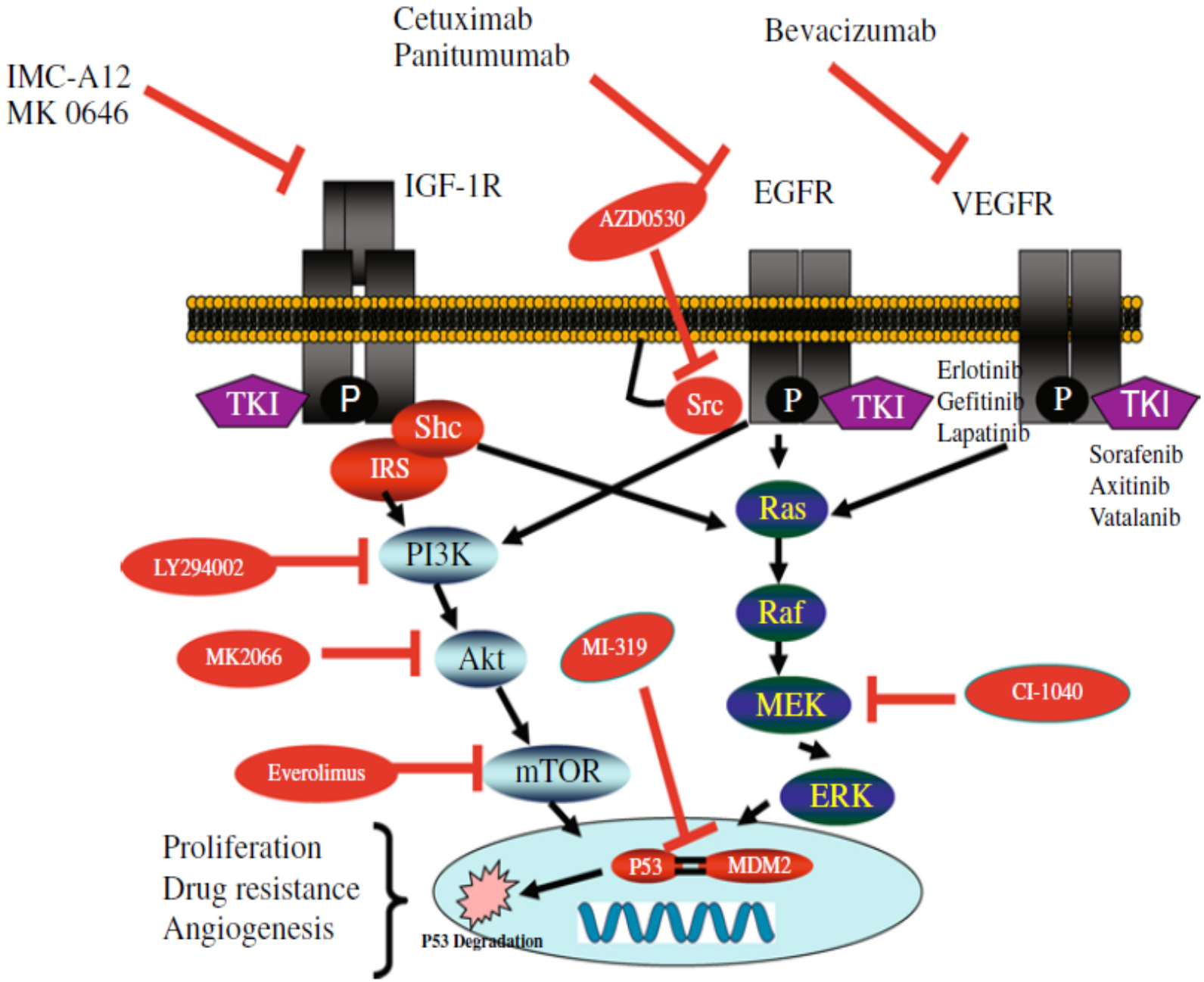
IMC-A12
MK 0646
Cetuximab
Panitumumab
Bevacizumab
IGF-1R
AZD0530
EGFR
VEGFR
TKI
P
Shc
IRS
Src
P
TKI
Erlotinib
Gefitinib
Lapatinib
P
TKI
Sorafenib
Axitinib
Vatalanib
Ras
LY294002
PI3K
Raf
MK2066
Akt
MI-319
MEK
CI-1040
Everolimus
mTOR
ERK
Proliferation
Drug resistance
Angiogenesis
P53
MDM2
P53 Degradation

Target	Drug	Phase	Combination therapy
IGF-1R	MK-0646	I/II	Gemcitabine
	AMG 479	I/II	AMG 655 (conatumumab)
	IMC-A12	I/II	Gemcitabine
	Cixutumumab	I/II	Gemcitabine
VEGFR	Vatalanib	I/II	Gemcitabine
	Vandetanib	I	Gemcitabine and Capecitabine
	Sorafenib	I/II	Everolimus
	Sunitinib	I	Gemcitabine
	Vatalanib	II	Single agent
EGFR	Gefitinib	I/II	Radiation/gemcitabine
	ARRY-334543	I/II	Gemcitabine
Src Kinase	Bosutinib	I/II	Gemcitabine (adjuvant)
	Dasatinib	I/II	Gemcitabine (adjuvant)
	AZD0530	I/II	Gemcitabine
c-Kit	Imatinib	I/II	Gemcitabine
	Masitinib	III	Gemcitabine
mTOR	Everolimus	I/II	Sorafenib
	Everolimus	I/II	Capecitabine/cetuximab
Akt	RX-0201(AKT anti-sense)	II	Gemcitabine
	Perifosine	II	Single agent
COX-2	Celecoxib	II	Gemcitabine
	Apricoxib	II	Gemcitabine
HSP-90	Tanespimycin	II	Gemcitabine
Hedgehogs	GDC-0449	II	Gemcitabine
Notch	MK0752	II/III	Gemcitabine
NF- κB	RTA 402	I/II	Gemcitabine
TRAIL	conatumumab (AMG655)	I/II	AMG 479
	Conatumumab (AMG655)	I/II	Capecitabine/Gemcitabine/radiation
	CS 108	II	Gemcitabine
HDAC	Vorinostat	I/II	Radiation
	Panobinostat	II	Bortezomib

EGFR Epidermal growth factor receptor; *VEGFR* Vascular endothelial growth factor; *IGF-1R* Insulin-like growth factor receptor; *mTOR* Mammalian target of rapamycin; *TKI* Tyrosine kinase inhibitor; *ERK* extracellular signal-regulated kinase; *PI3-Kinase* Phosphatidylinositide-3-Kinase; *HDAC* Histone deacetylase; *NF- κB* Nuclear factor kappa-light-chain-enhancer of activated B cells; *HSP-90* heat shock protein 90; *COX-2* Cyclooxygenase-2; *TRAIL* Tumour necrosis factor (TNF)-related apoptosis-inducing ligand

Table 2. Phase III and Some of the Phase II Clinical Trials of Targeted Agents in Pancreatic Cancer That Are Currently in Progress

Agents *(target)*	Clinical setting	Trial design	Treatment arms	Primary endpoints
Sorafenib	LAPC, metastatic (met.)	Phase III, RCT	Gem Gem+Sorafenib	PFS
Masitinib *(c-kit)*	LAPC, met.	Phase III, RCT	Gem+Placebo Gem+Masitinib	Overall survival (OS)
Erlotinib [E]	Resectable, adjuvant	Phase III, RCT 4-arms	I. Gem (5 cycles) II. Gem+E (5 cy) III. I or II+1 cycle IV. III+RT (5 wk)	OS in Gem +/− E group OS in Gem +/− RT group
Erlotinib [E], Sorafenib [S]	Unresectable PC	Phase II, single arm	E+S	PFS at 8 wk
GDC-0449 *(Shh)*	Recurrent (recur), met.	Phase II, D-blind, placebo controlled	Gem+Placebo Gem+DGC-0449	PFS
Cetuximab [C]	LAPC, met.	Phase II, single arm	Oxal+Irino+C	Efficacy
Panitumumab [P]	LAPC	Phase II, single arm	P+5FU-RT followed by P+G	Survival rate at 1 yr
Curcumin *(Nf-kB)*	LAPC, met., recur. PC	Phase II, single arm	Curcumin 8 gr/d	Survival, RR at 6 mo
Curcumin	Advanced PC, 1st line	Phase II, single arm	Curcumin+Gem	TTP
Sunitinib	Metastatic, maintainance after 6-mo chemotherapy	Phase II, randomized	Sunitinib Observation	PFS at 6-mo
Lapatinib [L]	LAPC, met. PC, 1st line	Phase II, single arm	L+Capecitabine	Survival rate at 6-mo
Lapatinib [L]	LAPC, met. PC, 2nd line	Phase II, single arm	L+Capecitabine	OS
Bevacizumab [B]	LAPC	Phase II, single arm	B+Gem+Oxal→ B+Oxal+5FU-RT	RR & TTP pre- and post-RT PFS, OS
Genistein *(Nf-kB)*	Resectable PC, neoadjuvant	Phase II, randomized	Genistein for 2 wk Observation	Changes in density of tumor microvessels
Erlotinib [E]	Metastatic PC	Phase II, single arm	E+Gem+Cisplatin	RR
Erlotinib [E]	Advanced PC, 1st line	Phase II, single arm	E+Gem+Oxal	RR
Erlotinib [E], Sorafenib [S]	Metastatic PC	Phase II, single arm	E+S+Gem	PFS at 4-mo
Sunitinib	Advanced PC, 1st line	Phase II, randomized	Gem Gem+Sunitinib	TTP
Bortezomib [Bor], Panobinostat [Pan]	Metastatic PC, Gem-resistant	Phase II, single arm	Bor+Pan	PFS
Erlotinib	Resectable, perioperative	Phase II, single arm	E (1 wk)→Surgery→ E+gem (6 mo)	Effect on predictive biomarkers
Cetuximab [C]	LAPC, unresectable	Phase II, single arm	C+RT (PACER)	PFS at 6-mo
Erlotinib	Resectable, adjuvant	Phase II, single arm	E+Capecitabine/RT→ E+Gem (4 mo)	PFS
Cetuximab [C]	LAPC, unresectable	Phase II, randomized	Gem-Cape (3 mo)→ UFT/LV+RT +/− C	OS at 1 yr
Pazopanib	Metastatic, 1st line	Phase II, single arm	Pazopanib+Gem	RR
Bevacizumab [B]	Advanced PC, 1st line	Phase II, single arm	B+Gem+5FU	PFS rate at 6-mo

Source: www.ClinicalTrials.gov.

LAPC, locally advanced pancreatic cancer; RCT, randomized controlled trial; Gem, gemcitabine; PFS, progression free survival; RT, radiotherapy; PC, pancreatic cancer; TTP, time to progression; RR, response rate; Oxal, oxaliplatin; UFT/LV; uftoral/leucovorin.

Angiogenesi	La pathway VEGF\VEGFR non ha dato soddisfazioni
EGFR	Cetuximab ha fallito , Panitumumab si sta studiando, Erlotinib con risultati positivi ma clinicamente non rilevanti
IGF-1R	In studio (problema di iperglicemia)
MAP Kinasi	MEK è considerato un target potenziale ma per farmaci usati in combinazione o "polivalenti"
PI3K/AKT/mTOR	Target interessanti per inibitori "polivalenti"
HedgeHog	E' una pathway che coinvolge la formazione dello stroma, forse fondamentale per la "penetrazione" dei chemioterapici.

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